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BICYCLO-PYRAZOLES ACTIVE AS KINASE INHIBITORS, PROCESS FOR
THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS
5 COMPRISING THEM

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to bicyclo-pyrazole derivatives active as kinase inhibitors
10 and, more in particular, it relates to pyrrolo-pyrazole and pyrazolo-azepine derivatives,
to a process for their preparation, to pharmaceutical compositions comprising them and
to their use as therapeutic agents, particularly in the treatment of diseases linked to
deregulated protein kinases.

Discussion of the Background

15 The malfunctioning of protein kinases (PKs) is the hallmark of numerous diseases.
A large share of the oncogenes and proto-oncogenes involved in human cancers code for
PKs. The enhanced activities of PKs are also implicated in many non-malignant
diseases such as benign prostate hyperplasia, familial adenomatosis, polyposis, neuro-
fibromatosis, psoriasis, vascular smooth cell proliferation associated with
20 atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical
stenosis and restenosis.

PKs are also implicated in inflammatory conditions and in the multiplication of viruses
and parasites. PKs may also play a major role in the pathogenesis and development of
neurodegenerative disorders.

25 For a general reference to PKs malfunctioning or deregulation see, for instance, Current
Opinion in Chemical Biology 1999, 3, 459-465.

Some pyrrolo-pyrazole or pyrazolo-azepine derivative are known in the art. Few
pyrazolo-azepine derivatives were studied (CAS 55:27362i, Yamamoto, H. et al, Bull.
Chem. Soc. Jap., 44(1), 153-8, 1971 and Moriya, T. et al; Bull. Chem. Soc. Jap., 41(1),
30 230-1, 1968). Some pyrrolo-pyrazole derivatives were disclosed in Elguero, J. et al;

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Bull. Soc. Chim. Fr.(4),1497-9 1971 and the antibacterial activity of some other pyrrolo-pyrazole derivatives was shown in WO01/042242 and JP06073056.

SUMMARY OF THE INVENTION

The present inventors have now discovered that some pyrrolo-pyrazoles and pyrazolo-azepines are endowed with multiple protein kinase inhibiting activity and are thus useful in therapy in the treatment of diseases caused by and/or associated with deregulated protein kinases.

As such, it is an object of the invention to provide compounds, which are useful as therapeutic agents against a host of diseases caused by a deregulated protein kinase activity.

It is another object to provide compounds endowed with multiple protein kinase inhibiting activity.

More specifically, the pyrrolo-pyrazoles and pyrazolo-azepines of this invention are useful in the treatment of a variety of cancers including, but not limited to: carcinoma such as bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma; hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma and schwannomas; other tumors, including 20 melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratocanthoma, thyroid follicular cancer and Kaposi's sarcoma.

Due to the key role of PKs in the regulation of cellular proliferation, these pyrrolo-pyrazoles and pyrazolo-azepines are also useful in the treatment of a variety of cell proliferative disorders such as, for instance, benign prostate hyperplasia, familial adenomatosis, polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell

proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis.

The compounds of the invention can be useful in the treatment of Alzheimer's disease, as suggested by the fact that cdk5 is involved in the phosphorylation of tau protein (J.

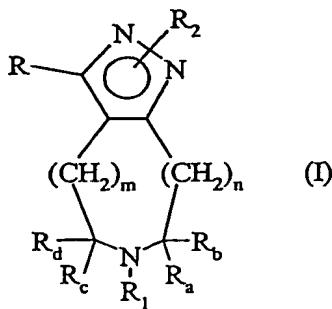
5 Biochem., 117, 741-749, 1995).

The compounds of this invention, as modulators of apoptosis, may also be useful in the treatment of cancer, viral infections, prevention of AIDS development in HIV-infected individuals, autoimmune diseases and neurodegenerative disorders.

10 The compounds of this invention may be useful in inhibiting tumor angiogenesis and metastasis.

15 The compounds of the invention are useful as cyclin dependent kinase (cdk) inhibitors and also as inhibitors of other protein kinases such as, for instance, protein kinase C in different isoforms, Met, PAK-4, PAK-5, ZC-1, STLK-2, DDR-2, Aurora 1, Aurora 2, Bub-1, PLK, Chk1, Chk2, HER2, raf1, MEK1; MAPK, EGF-R, PDGF-R, FGF-R, IGF-R, VEGF-R; PI3K, weel kinase, Src, Abl, Akt, ILK, MK-2, IKK-2, Cdc7, Nek, and thus be effective in the treatment of diseases associated with other protein kinases.

20 Accordingly, the present invention provides a method for treating diseases caused by and/or associated with an altered protein kinase activity which comprises administering to a mammal in need thereof an effective amount of a pyrrolo-pyrazole or pyrazolo-azepine derivative represented by formula (I):



25 wherein R represents hydrogen or halogen atom, or an optionally substituted group selected from aryl C₂-C₆ alkenyl, (heterocycl) C₂-C₆ alkenyl, aryl C₂-C₆ alkynyl, or (heterocycl) C₂-C₆ alkynyl group, -R', -COR', -COOR', -CN, -CONR'R'', -OR', -S(O)_qR', -SO₂NR'R'', -B(OR'')₂, -SnR'''', wherein R' and R'', the same or different, independently represent hydrogen atom or an optionally further substituted straight or

branched C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, saturated or unsaturated C₃-C₆ cycloalkyl, aryl, heterocyclyl, aryl C₁-C₆ alkyl or (heterocyclyl)C₁-C₆ alkyl; R''' represents hydrogen,

5 C₁-C₆ alkyl, or R''', together with the two oxygen and the boron atoms, forms a saturated or unsaturated C₅-C₈ (hetero)cycloalkyl, optionally benzocondensed or substituted, and R''' represents C₁-C₆ alkyl;

R₁ represents hydrogen atom or an optionally substituted group selected from -R', -CH₂R', -COR', -COOR', -CONR'R'', -C(=NH)NHR', -S(O)_qR', or -SO₂NR'R'', wherein R' and R'' are as defined above;

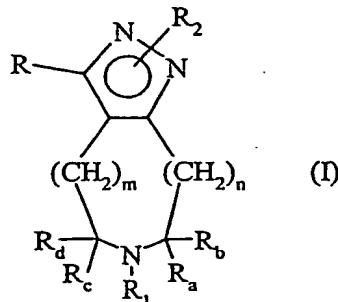
10 R₂ represents hydrogen atom, -COR', -COOR', -CONR'R'', -S(O)_qR', -SO₂NR'R'', C₁-C₆ alkyl or (heterocyclyl)C₁-C₆ alkyl group, wherein R' and R'' are as defined above; R_a, R_b, R_c and R_d, being the same or different, independently represent hydrogen atom, an optionally further substituted straight or branched C₁-C₆ alkyl, aryl, heterocyclyl, aryl C₁-C₆ alkyl, (heterocyclyl)C₁-C₆ alkyl or -CH₂OR' group, wherein R' is as above defined, or R_a and R_b and/or R_c and R_d, taken together with the carbon atom to which they are bonded, form an optionally substituted, saturated or unsaturated, C₃-C₆ cycloalkyl group; q is 0, 1 or 2; m and n, each independently, represents 0, 1 or 2, provided that m + n is 0 or equal to 2; or a pharmaceutically acceptable salt thereof.

In a preferred embodiment of the method described above, the disease caused by and/or 20 associated with an altered protein kinase activity is selected from the group consisting of cancer, cell proliferative disorders, Alzheimer's disease, viral infections, auto-immune diseases and neurodegenerative disorders.

Specific types of cancer that may be treated according to the invention include carcinoma, squamous cell carcinoma, hematopoietic tumors of myeloid or lymphoid 25 lineage, tumors of mesenchymal origin, tumors of the central and peripheral nervous system, melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoanthoma, thyroid follicular cancer and Kaposi's sarcoma.

In another preferred embodiment of the method described above, the cell proliferative disorder is selected from the group consisting of benign prostate hyperplasia, familial 30 adenomatosis polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis

glomerulonephritis and post-surgical stenosis and restenosis. In addition, the method object of the present invention, provides tumor angiogenesis and metastasis inhibition. The present invention also provides a pyrrolo-pyrazole or pyrazolo-azepine derivative represented by formula (I):



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wherein R represents hydrogen or halogen atom, or an optionally substituted group selected from aryl C₂-C₆ alkenyl, (heterocyclyl) C₂-C₆ alkenyl, aryl C₂-C₆ alkynyl, or (heterocyclyl) C₂-C₆ alkynyl group, -R', -COR', -COOR', -CN, -CONR'R'', -OR', -S(O)_qR', -SO₂NR'R'', -B(OR'')₂, -SnR'''', wherein R' and R'', the same or different, independently represent hydrogen atom or an optionally further substituted straight or branched C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, saturated or unsaturated C₃-C₆ cycloalkyl, aryl, heterocyclyl, aryl C₁-C₆ alkyl or (heterocyclyl)C₁-C₆ alkyl; R''' represents hydrogen, C₁-C₆ alkyl, or R'', together with the two oxygen and the boron atoms, forms a saturated or unsaturated C₅-C₈ (hetero)cycloalkyl, optionally benzocondensed or substituted, and R''' represents C₁-C₆ alkyl; R₁ represents hydrogen atom or an optionally substituted group selected from -R', -CH₂R', -COR', -COOR', -CONR'R'', C(=NH)NHR', -S(O)_qR', or -SO₂NR'R'', wherein R' and R'' are as defined above; R₂ represents hydrogen atom, -COR', -COOR', -CONR'R'', -S(O)_qR', -SO₂NR'R'', C₁-C₆ alkyl or (heterocyclyl)C₁-C₆ alkyl group, wherein R' and R'' are as defined above; R_a, R_b, R_c and R_d, being the same or different, independently represent hydrogen atom, an optionally further substituted straight or branched C₁-C₆ alkyl, aryl, heterocyclyl, aryl C₁-C₆ alkyl, (heterocyclyl)C₁-C₆ alkyl or -CH₂OR' group, wherein R' is as above defined, or R_a and R_b and/or R_c and R_d, taken together with the carbon atom to which they are bonded, form an optionally substituted, saturated or unsaturated, C₃-C₆

cycloalkyl group; q is 0, 1 or 2; m and n, each independently, represents 0, 1 or 2, provided that m + n is 0 or equal to 2; with the following further provisos:

- when m and n are both 1, R is hydrogen atom or hydroxy group and R_a, R_b, R_c and R_d are all hydrogen atoms, then R₁ is not hydrogen atom, acetyl, benzyl or 5 ethoxycarbonyl group;
- when m is 2 and n is 0, R, R_a, R_b, R_c and R_d are all hydrogen atoms, then R₁ is not hydrogen atom or ethoxycarbonyl group;
- when m and n are both 0, R, R_a, R_b, R_c and R_d are all hydrogen atoms, then R₁ is not 10 hydrogen atom, phenyl-oxazolidinone, quinoline, pyridobenzoxazine or naphthyridine group;
- when m and n are both 0, R is propyl, R_a, R_b, R_c and R_d are all hydrogen atoms, then R₁ is not phenyl-oxazolidinone group and
- when m and n are both 0, R is hydroxy, methyl or ethyl group and R_a, R_b, R_c and R_d 15 are all hydrogen atoms, then R₁ is not a methoxycarbonyl group;

15 or a pharmaceutically acceptable salt thereof.

The pyrrolo-pyrazole and pyrazolo-azepine derivatives of formula (I), object of the invention, are obtainable through a synthetic process comprising well known reactions carried out according to conventional techniques, as well as through an extremely versatile solid-phase and/or combinatorial process, being all comprised within the scope 20 of the invention.

The present invention also provides a pharmaceutical composition comprising the pyrrolo-pyrazole or pyrazolo-azepine derivatives of formula (I) and at least one pharmaceutically acceptable excipient, carrier or diluent.

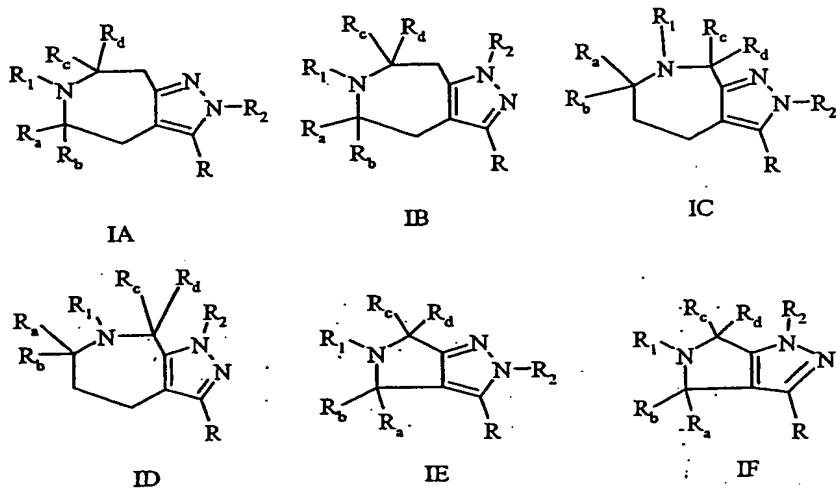
25 A more complete appreciation of the invention and many of the attendant advantages thereof will be readily obtained as the same becomes better understood by reference to the following detailed description.

DETAILED DESCRIPTION OF THE INVENTION

30 The compounds of formula (I), object of the present invention, may have asymmetric carbon atoms and may therefore exist either as racemic admixtures or as individual optical isomers. Accordingly, all the possible isomers and their admixtures and of both the metabolites and the pharmaceutically acceptable bio-precursors (otherwise referred

to as pro-drugs) of the compounds of formula (I), as well as any therapeutic method of treatment comprising them, are also within the scope of the present invention.

As it will be readily appreciated, depending on the values of m and n, the ring condensed to the pyrazole may consist of 5 or 7 atoms; as to the pyrazole ring, two isomers are possible and therefore the R₂ substituent may be on one of the two nitrogens. Accordingly, in the present invention and unless otherwise indicated, the general formula I comprises the compounds of formula IA, IB, IC, ID, IE and IF:



10 wherein R, R₁, R₂, R_a, R_b, R_c and R_d are as defined above.

As used herein, unless otherwise specified, with the term straight or branched C₁-C₆ alkyl, we intend a group such as, for instance, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl, isohexyl, and the like. With the term aryl we intend an aromatic carbocycle such as, for instance, phenyl, biphenyl, 1-naphthyl, 2-naphthyl, and the like. Clearly, aryl groups may also refer to aromatic carbocyclic further fused or linked to non aromatic heterocyclic rings, typically 5 to 7 membered heterocycles.

With the term heterocyclyl, hence encompassing aromatic heterocycles, we further intend a saturated or partially unsaturated 5 to 7 membered carbocycle wherein one or more carbon atoms are replaced by heteroatoms such as nitrogen, oxygen and sulphur, for instance, 1,3-dioxolane, pyran, thiophene, furan, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, pyrrolidine, pyrrolidine, imidazolidine, imidazoline, piperidine, piperazine, morpholine,

tetrahydrofuran, tetrahydropyran, tetrahydrothiopyran, imidazolidine, pyrazolidine, pyrazoline, piperidine, azabicyclononane and the like.

Also the heterocycles may be optionally fused and, unless otherwise indicated, we intend any of the above defined heterocycles further condensed, through any one of the 5 available bonds, with 5- or 6-membered, saturated or unsaturated heterocycl ring, or to a $C_3 - C_6$ cycloalkyl ring, or to a benzene or naphthalene ring such as, for instance, quinoline, isoquinoline, chroman, chromene, thionaphthalene, indoline, and the like.

With the term $C_2 - C_6$ alkenyl, we intend a straight or branched alkenyl group such as vinyl, allyl, crotyl, 2-methyl-1-propenyl, 1-methyl-1-propenyl, butenyl, pentenyl. The 10 $C_2 - C_6$ alkynyl group is a straight or branched alkynyl group such as ethynyl, propargyl, 1-propynyl, 1-butynyl, 2-butynyl.

With the term saturated or unsaturated $C_3 - C_6$ cycloalkyl group we intend, for instance, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentenyl, cyclohexenyl, and the like. Unless otherwise specified, saturated or unsaturated cycloalkyl groups can be 15 further condensed with 1 or 2 benzene rings are, for instance, 1,2,3,4-tetrahydro-naphthalene-2-yl, fluorene-9-yl, and the like.

The term " $C_5 - C_8$ (hetero)cycloalkyl" as used herein refers to a 5- to 8-membered, substituted or unsubstituted, saturated or unsaturated heterocycl ring, containing at least one boro and two oxygen atoms, any ring carbon may be oxidized as a carbonyl, and 20 wherein said ring may be optionally fused to a second 5- or 6-membered, saturated or unsaturated heterocycl ring, or to a $C_3 - C_7$ cycloalkyl ring, or to a benzene or naphthalene ring.

The term "aryl $C_1 - C_6$ alkyl" refer to a straight or branched chain alkyl moiety having 25 from 1 to 6 carbon atoms substituted with at least one aryl group as defined above, such as, for instance, benzyl, phenylethyl, benzhydryl, benzyloxy and the like. The "aryl $C_2 - C_6$ alkenyl group" is an alkenyl group of 2 to 6 carbon atoms linked to a monocyclic or bicyclic aromatic hydrocarbon group of 6 to 10 carbon atoms. Examples of aryl alkenyl groups are styryl, 2-phenyl-1-propenyl, 3-phenyl-2-butenyl, 2-naphthylethenyl. The "aryl $C_2 - C_6$ alkynyl group" is an alkynyl group of 2 to 6 carbon atoms linked to a 30 monocyclic or bicyclic aromatic hydrocarbon group of 6 to 10 carbon atoms. Examples of aryl alkynyl groups are 2-phenylethynyl, 2-naphthylethynyl.

The (heterocyclyl) C₁-C₆ alkyl group is an alkyl group of 1 to 6 carbon atoms linked to a heterocyclyl group. The (heterocyclyl) C₂-C₆ alkenyl group is an alkenyl group of 2 to 6 carbon atoms linked to a heterocyclic group. The (heterocyclyl) C₂-C₆ alkynyl group is an alkynyl group of 2 to 6 carbon atoms linked to a heterocyclic group.

5 From all of the above, it is clear to the skilled man that any of the groups or substituents being defined, for instance, as arylalkyl, alkoxy, cycloalkoxy, aryloxy, arylalkyloxy and the like, have to be construed from the names of the groups from which they originate. As an example, unless specifically noted otherwise, any arylalkyloxy group has to be intended as an alkyloxy wherein the alkyl moiety is substituted by at least one aryl, both 10 aryl and alkyl being as above defined.

With the term halogen atom, we intend fluoro, bromo, chloro or iodo atom.

The term "optionally substituted" means that the group may be substituted or unsubstituted; the substituents which may be present in the alkyl, cycloalkyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkoxy, aryloxy, cycloalkoxy, alkenyl, alkynyl or

15 heterocyclyl groups in any of the above definitions include the following:

- halo (i.e., fluoro, bromo, chloro or iodo);
- hydroxy;
- oxo (i.e., =O);
- nitro;
- 20 - azido;
- mercapto (i.e., -SH), and acetyl or phenylacetyl esters thereof (i.e., -SCOCH₃ and -SCOCH₂C₆H₅);
- amino (i.e., -NH₂ or -NHR^I or -NRR^IR^{II}, wherein R^I and R^{II}, which are the same or different, are straight or branched C₁-C₆ alkyl, phenyl, biphenyl (i.e., -C₆H₄-C₆H₅), or 25 benzyl groups, optionally substituted by hydroxy, methoxy, methyl, amino, methylamino, dimethylamino, chloro or fluoro; or R^I and R^{II} taken together with the nitrogen atom to which they are attached form a heterocyclic ring such as morpholino, pyrrolidino, piperidino, pyperazino or N-methylpyperazino;
- guanidino, i.e., -NHC(=NH)NH₂;
- 30 - formyl (i.e. -CHO);
- cyano;

- carboxy (i.e. -COOH), or esters thereof (i.e., -COOR^I), or amides thereof (i.e., -CONH₂, -CONHR^I or -CONHR^IR^{II}), wherein R^I and R^{II} are as defined above, and including morpholino-amides, pyrrolidino-amides, and carboxymethylamides -CONHCH₂COOH;
- sulfo (i.e., -SO₃H);

5 - acyl, i.e., -C(O)R^I, wherein R^I is as defined above, including monofluoroacetyl, difluoroacetyl, trifluoroacetyl;

- carbamoyloxy (i.e., -OCONH₂) and N-methylcarbamoyloxy;
- acyloxy, i.e., -OC(O)R^I wherein R^I is as defined above, or formyloxy;
- acylamino, i.e., -NHC(O)R^I, or -NHC(O)OR^I, wherein R^I is as defined above or is a

10 group -(CH₂)_tCOOH where t is 1, 2 or 3;

- ureido, i.e., -NH(CO)NH₂, -NH(CO)NHR^I, -NH(CO)NR^IR^{II}, wherein R^I and R^{II} are as defined above, including -NH(CO)-(4-morpholino), -NH(CO)-(1-pyrrolidino), -NH(CO)-(1-piperazino), -NH(CO)-(4-methyl-1-piperazino);
- sulfonamido, i.e., -NHSO₂R^I wherein R^I is as defined above;

15 - a group -(CH₂)_tCOOH, and esters and amides thereof, i.e., -(CH₂)_tCOOR^I and -(CH₂)_tCONH₂, -(CH₂)_tCONHR^I, -(CH₂)_tCONR^IR^{II}, wherein t, R^I and R^{II} are as defined above;

- a group -NH(SO₂)NH₂, -NH(SO₂)NHR^I, -NH(SO₂)NR^IR^{II}, wherein R^I and R^{II} are as defined above, including -NH(SO₂)-(4-morpholino), -NH(SO₂)-(1-pyrrolidino), -

20 NH(SO₂)-(1-piperazino), -NH(SO₂)-(4-methyl-1-piperazino);

- a group -OC(O)OR^I, wherein R^I is as defined above;
- a group -OR^I, wherein R^I is as defined above, including -OCH₂COOH;
- a group -O-CH₂-O-, methylenedioxy or -O-CH₂-CH₂-O-, ethylenedioxy;
- a group -SR^I, wherein R^I is as defined above, including -SCH₂COOH;

25 - a group -S(O)R^I, wherein R^I is as defined above;

- a group -S(O₂)R^I, wherein R^I is as defined above;
- a group -SO₂NH₂, -SO₂NHR^I, or -SO₂NR^IR^{II}, wherein R^I and R^{II} are as defined above;
- C₁-C₆ alkyl or C₂-C₆ alkenyl;
- C₃-C₇ cycloalkyl;

30 - substituted methyl selected from chloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, aminomethyl, N,N-dimethylaminomethyl, azidomethyl, cyanomethyl,

carboxymethyl, sulfomethyl, carbamoylmethyl, carbamoyloxymethyl, hydroxymethyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, tert-butoxycarbonylmethyl and guanidinomethyl.

When present, carboxy, hydroxy, mercapto and amino groups may be either free or in a 5 protected form. Protected forms of said groups are any of those generally known in the art. Preferably, carboxy groups are protected as esters thereof, in particular methyl, ethyl, tert-butyl, benzyl, and 4-nitrobenzyl esters. Preferably, hydroxy groups are protected as silyl-ethers, ethers or esters thereof, in particular trimethyl silyl, tert-butyldiphenyl silyl, triethyl silyl, triisopropyl silyl or tert-butyldimethylsilyl ethers, methoxymethyl ethers, 10 tetrahydropyranyl ethers, benzyl ethers, acetates or benzoates. Preferably, mercapto groups are protected as thioethers or thioesters, in particular tert-butyl thioethers, thioacetates or thiobenzoates. Preferably, amino groups are protected as carbamates, e.g. tert-butoxycarbonyl derivatives, or as amides, e.g. acetamides and benzamides.

Furthermore, hydrates, solvates of compounds of formula (I), and physiologically 15 hydrolyzable derivatives (i.e., prodrugs) of compounds of formula (I) are included within the scope of the present invention.

Pharmaceutically acceptable salts of the compounds of formula (I) are the acid addition salts with inorganic or organic, e.g. nitric, hydrochloric, hydrobromic, sulphuric, perchloric, phosphoric, acetic, trifluoroacetic, propionic, glycolic, lactic, oxalic, 20 malonic, malic, maleic, tartaric, citric, benzoic, cinnamic, mandelic, methanesulphonic, isethionic and salicylic acid, as well as the salts with inorganic or organic bases, e.g. alkali or alkaline-earth metals, especially sodium, potassium, calcium or magnesium hydroxides, carbonates or bicarbonates, acyclic or cyclic amines, preferably methylamine, ethylamine, diethylamine, triethylamine or piperidine.

Preferred compounds of formula (I) are the compounds wherein R is H, I, Br, Cl, F, 25 aryl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -B(OR'')₂, -COR', -CONR'R'', -CN, SO₂R', OR', SR', and R₁ is H, C₁-C₆ alkyl, aryl, -COR', -CONR'R'', -COOR', -SO₂R', or -SO₂NR'R'', and R₂ is H, -COOR', -COR', -CONR'R'', C₁-C₆ alkyl, -SO₂R', or -SO₂NR'R'', (heterocycl) C₁-C₆ alkyl group, wherein R' and R'', the same or different, are selected 30 from hydrogen or optionally substituted straight or branched C₁-C₆ alkyl, aryl or aryl C₁-C₆ alkyl groups;

R_a , R_b , R_c and R_d , the same or different, are selected from hydrogen or straight or branched C_1 - C_3 alkyl or, taken together with the carbon atom to which they are bonded form a C_3 - C_6 cycloalkyl group.

Other preferred compounds of formula (I) are the compounds wherein R is selected 5 from aryl, heterocyclyl, -COR', -CONR'R", wherein R' and R", the same or different, are selected from hydrogen or optionally substituted straight or branched C_1 - C_6 alkyl, aryl or aryl C_1 - C_6 alkyl groups.

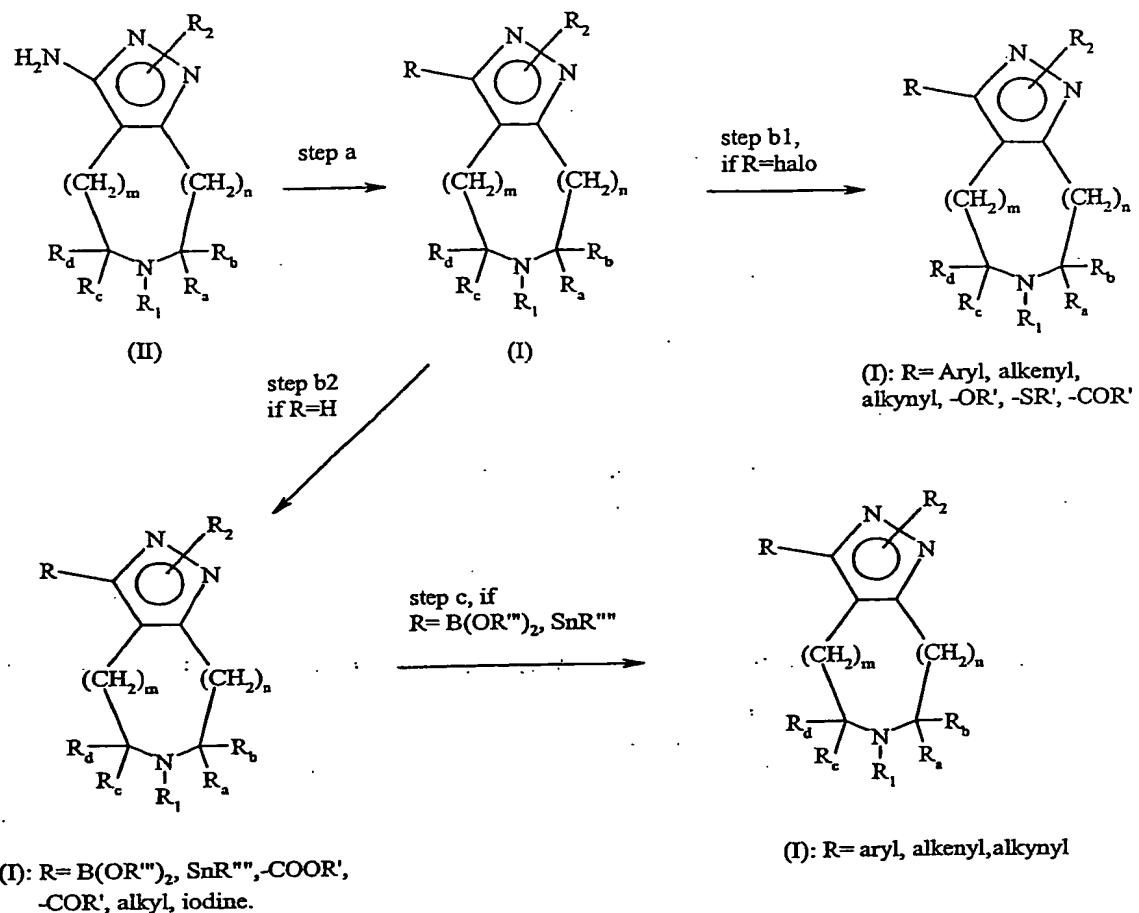
Other preferred compounds of formula (I) are the compounds wherein R_1 is selected 10 from H, C_1 - C_6 alkyl, aryl, -COR', -CONR'R", COOR', -SO₂R' or -SO₂NR'R", wherein R' and R", the same or different, are selected from hydrogen or optionally substituted straight or branched C_1 - C_6 alkyl, aryl or aryl C_1 - C_6 alkyl groups.

Another preferred class of compounds of formula (I) are the compounds wherein R_2 is 15 H,

-COOR', -CONR'R", C_1 - C_6 alkyl, wherein R' and R", the same or different, are selected from hydrogen or optionally substituted straight or branched C_1 - C_6 alkyl, aryl or aryl C_1 - C_6 alkyl groups.

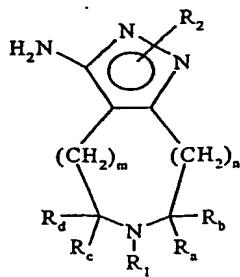
As formerly indicated, it is a further object of the invention a process for preparing the compounds of formula (I) and pharmaceutically acceptable salts thereof.

General reaction scheme



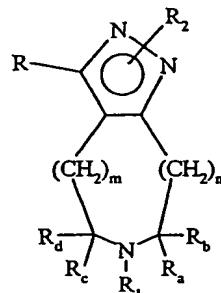
In particular, the present invention provides a process which comprises:

a) submitting a compound of formula (II)



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wherein R_1 is as defined above but not hydrogen, and $\text{R}_a, \text{R}_b, \text{R}_c, \text{R}_d, \text{R}_2, \text{m}$ and n are as defined above, to diazotation and subsequent appropriate quenching, thus obtaining a compound of formula (I)



(I)

wherein R_1 is as defined above but not hydrogen; R_a , R_b , R_c , R_d , R_2 , m and n are as defined above, and R is hydrogen, iodine, bromine, chlorine or fluorine atom or a CN group;

5 b1) converting a thus obtained compound of formula (I) wherein R is I, Br, Cl into another compound of formula (I) wherein R is an optionally substituted aryl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, $-SR'$, $-OR'$ or $-COR'$ wherein R' is as defined above;

10 b2) converting a compound of formula (I) wherein R is hydrogen into another compound of formula (I) wherein R is $-B(OR'')_2$, $-SnR'''$, $-COOR'$, $-COR'$, C_1 - C_6 alkyl or iodine, wherein R' , R'' and R''' are as defined above;

15 c) converting a compound of formula (I) wherein R is $-B(OR'')_2$ or $-SnR'''$ as above defined into another compound of formula (I) wherein R is an optionally substituted aryl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl;

 d) optionally converting a compound of formula (I) into another different compound of formula (I),

and, if desired, converting a compound of formula (I) into a pharmaceutically acceptable salt thereof or converting a salt into the free compound (I).

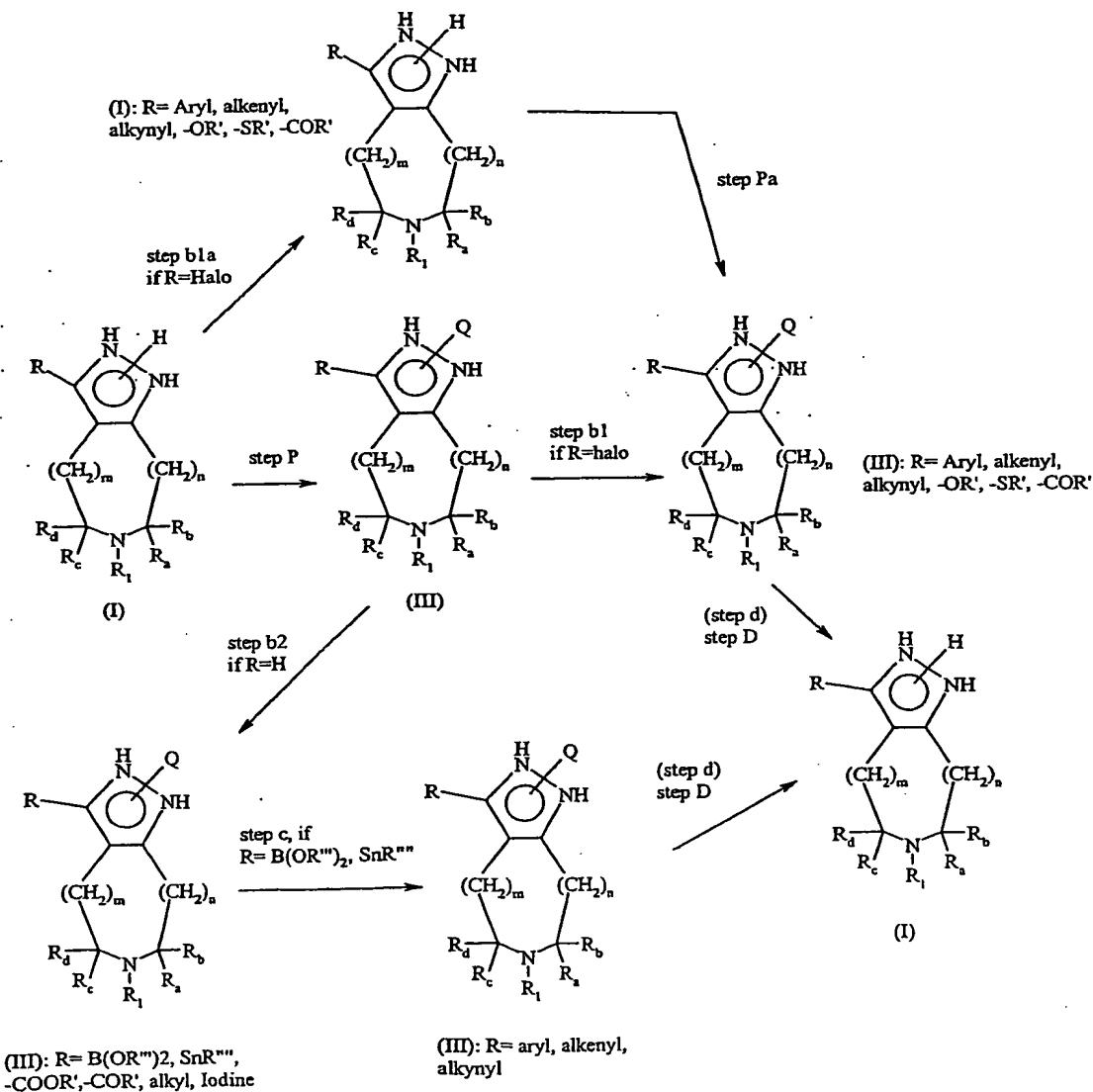
The above process can be carried out according to well known methods. It is clear to the person skilled in the art that if a compound of formula (I), prepared according to the above process, is obtained as an admixture of isomers, their separation into the single isomers of formula (I), carried out according to conventional techniques, is still within the scope of the present invention.

Likewise, the salification of a compound of formula (I) or the conversion of its salt into the free compound (I), carried out according to well-known procedures in the art, are still within the scope of the invention.

According to a preferred aspect of the process of the invention avoiding the unwanted by-products formation, a compound of formula (I), obtained according to step a above, could be first supported onto a suitable solid support, such as resin and then, after the reactions as per steps b1, b2, c and d above described, reconverted into a compound of formula (I).

5

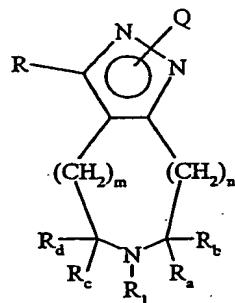
General reaction scheme



It is therefore a further object of the invention a process for preparing a compound of formula (I) as defined above, which process comprises:

either

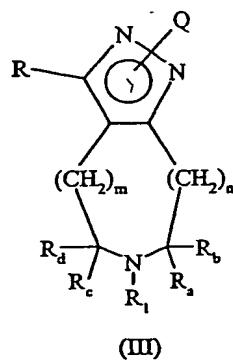
b1a) converting a compound of formula (I) into another compound of formula (I)
 5 wherein R has the above reported meanings resulting from step b1 and R₁, R_a, R_b, R_c, R_d, m and n are as defined above analogously to step b1 above described and
 Pa) reacting the resultant compound of formula (I) wherein R, R_a, R_b, R_c, R_d, m and n are as defined above, R₁ is as described above but not hydrogen and R₂ is hydrogen, with a suitable solid support so as to obtain a compound of formula (III)



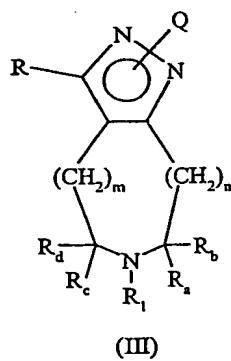
(III)

10 wherein R, R_a, R_b, R_c, R_d, m and n are as defined above, R₁ is as defined above but not hydrogen, and Q is a solid support, or
 P) reacting a compound of formula (I) wherein R, R_a, R_b, R_c, R_d, m and n are as defined above, R₁ is as defined above but not hydrogen and R₂ is hydrogen, with a suitable solid support so as to obtain a compound of formula (III) as defined above and
 15 B) then, analogously to steps b1, b2, c and d above described, optionally converting a thus obtained compound of formula (III) into another compound of formula (III) wherein R has the above reported meanings for steps b1, b2, c and d and R₁, R_a, R_b, R_c, R_d, m and n are as defined above;
 20 D) cleaving the resultant compound of formula (III) so as to eliminate the solid support and to obtain the desired compound of formula (I);
 E) optionally converting a compound of formula (I) into another different compound of formula (I),
 and, if desired, converting a compound of formula (I) into a pharmaceutically acceptable salt thereof or converting a salt into the free compound (I) as described above.
 25

It is a further object of the present invention to provide useful intermediates of formula III



wherein R, R₁, R_a, R_b, R_c, R_d, m and n are as defined above, and Q is a solid support,
 5 more preferably a residue derived from a resin selected from the group consisting of isocyanate polystyrenic resin, 2-chloro-trityl chloride resin, trityl chloride resin, p-nitrophenyl carbonate Wang resin and the bromo-4-methoxyphenyl)methyl polystyrene. A process for the preparation of a compound of formula (III) as defined above is also provided, which process comprises:
 10 either
 b1a) converting a compound of formula (I) into another compound of formula (I)
 wherein R has the above reported meanings resulting from step b1 and R₁, R_a, R_b, R_c, R_d, m and n are as defined above, analogously to step b1 above described and
 Pa) reacting the resultant compound of formula (I) wherein R, R_a, R_b, R_c, R_d, m and n
 15 are as defined above, R₁ is as defined above but not hydrogen and R₂ is hydrogen, with a suitable solid support so as to obtain a compound of formula (III)



wherein R, R_a, R_b, R_c, R_d, m and n are as defined above, R₁ is as defined above but not hydrogen, and Q is a solid support, or

P) reacting a compound of formula (I) wherein R, R_a, R_b, R_c, R_d, m and n are as defined above, R₁ is as described above but not hydrogen and R₂ is hydrogen, with a suitable

5 solid support so as to obtain a compound of formula (III) as defined above and

B) then, analogously to steps b1, b2, c and d above described, optionally converting a thus obtained compound of formula (III) into another compound of formula (III) wherein R has the above reported meanings for steps b1 to d and R₁, R_a, R_b, R_c, R_d, m and n are as defined above.

10 According to step a) of the process, a compound of formula (I) wherein R is hydrogen, I, Br, Cl, F, CN, and R₁ is as defined above but not hydrogen, and R_a, R_b, R_c, R_d, R₂, m and n are as defined above, may be prepared by reacting a compound of formula (II), wherein R₁ is as defined above but not hydrogen, and R_a, R_b, R_c, R_d, R₂, m and n are as defined above, with organic or inorganic nitrites such as sodium nitrite or isopentyl nitrite, in the presence of a suitable hydrogen source, such as H₃PO₂, thiophenol, sodium stannite, Bu₃SnH, Et₃SiH, or of a suitable halogenating or cyanating agent such as tetrabutylammonium iodide and/or iodine, tetrabutylammonium bromide and/or bromine, tetrabutylammonium chloride and/or chlorine, CuBr, CuCl, CuI, CuCN, sodium tetrafluoroborate, ammonium tetrafluoroborate, in aqueous acidic solution at various concentrations such as diluted chloridic acid or diluted citric acid, or in organic solvents such as tetrahydrofuran, 1,4-dioxan, dichloromethane, chloroform, toluene, acetonitrile, ethylacetate, acetone, dimethylformamide, ethanol, methanol, water at a temperature ranging from about -78° C to reflux, for a suitable time ranging from 5 min to 72 hours. More preferably, the step a) is carried out on compounds of the formula (II)

20 wherein R₂ is not hydrogen atom.

25 According to step b1) of the process, a compound of formula (I) wherein R is an optionally substituted aryl or C₂-C₆ alkenyl group, and R₁, R₂, R_a, R_b, R_c, R_d, m and n are as defined above, can be obtained by reacting a compound of formula (I), wherein R is halogen atom, and R₁, R₂, R_a, R_b, R_c, R_d, m and n are as defined above, with a suitable aryl boronic acid or ester, alkenyl boronic acid or ester, arylstannane, in the presence of a suitable catalysing agent such as palladium(0)tetrakis, bis

triphenylphosphine palladium(II) dichloride, bis tricyclohexylphosphine palladium(II) dichloride, bis tri-o-tolylphosphine palladium(II) dichloride, palladium(II) acetate, tris(dibenzylideneacetone) dipalladium(0), [1,1'-bis(diphenylphosphino) ferrocene] dichloropalladium(II), [1,1'-bis(diphenylphosphino) ferrocene] dichloronickel(II), 1,4-bis(diphenylphosphino) butane palladium(II), and of a suitable base such as sodium carbonate, cesium carbonate, potassium carbonate, potassium phosphate, triethylamine, sodium hydroxide, cesium fluoride, potassium tert-butyrate, sodium ethylate, potassium acetate, in a suitable solvent, such as 1,4-dioxan, tetrahydrofuran, DMF (N,N-dimethylformamide), dimethoxyethane, toluene, methanol, ethanol, water, N-methylpyrrolidone, and, when needed, adding a suitable ligand, such as tributylphosphine, triphenylphosphine, tri-o-tolylphosphine, tricyclohexyl, biphenyl(dicyclohexyl) phosphine, biphenyl(ditert-butyl) phosphine, diphenylphosphine ferrocene, and/or Cu(I) salts such as CuI, Cu(I)thiophene-2-carboxylate at a temperature ranging from room temperature to reflux, for a suitable time ranging from 15 minutes to 15 72 hours.

According to step b1) of the process, a compound of formula (I) wherein R is an optionally substituted C₁-C₆ alkynyl, and R₁, R₂, R_a, R_b, R_c, R_d, m and n are as defined above, can be obtained by reacting a compound of formula (I), wherein R is halogen, and R₁, R₂, R_a, R_b, R_c, R_d, m and n are as defined above, with a suitable alkyne under the condition of the Sonogashira's reaction, in the presence of a suitable catalysing agent such as bistriphenylphosphine palladium(II) dichloride, palladium(0) tetrakis, palladium(II) acetate, tris(dibenzylideneacetone) dipalladium(0), and of a suitable Cu(I) salt, such as CuI, and in presence of a suitable base such as sodium carbonate, potassium carbonate, cesium carbonate, potassium phosphate, triethylamine, diisopropylamine, pyridine, in a suitable solvent, such as 1,4-dioxan, tetrahydrofuran, DMF, dimethoxyethane, toluene, ethanol, methanol, and, if needed, adding a suitable ligand such as triphenylphosphine, tri-o-tolylphosphine, tricyclohexyl, diphenylphosphineferrocene, at a temperature ranging from room temperature to reflux, for a suitable time ranging from 15 minutes to 72 hours.

30 According to step b1) of the process, a compound of formula (I) wherein R is SR', OR', and R₁, R₂, R_a, R_b, R_c, R_d, R', m and n are as defined above, can be obtained by reacting

a compound of formula (I), wherein R is halogen, and R₁, R₂, R_a, R_b, R_c, R_d, m and n are as defined above, with a suitable alcohol or thiol R'OH or R'SH wherein R' is as above defined, in the presence of a suitable base, such as potassium carbonate, sodium carbonate, cesium carbonate, potassium hydroxide, sodium hydroxide, sodium hydride, 5 sodium methylate, sodium tert-butyrate, diisopropylethylamine, pyridine, piperidine, N-methylmorpholine, dimethylaminopyridine, and, if needed, in the presence of catalysing agent, such as bis tricyclohexylphosphine palladium(II) dichloride, bis tri-o-tolylphosphine palladium(II) dichloride, palladium(II) acetate, tris(dibenzylideneacetone) dipalladium(0), [1,1'-bis(diphenylphosphino) ferrocene] 10 dichloropalladium(II), and of a suitable ligand, such as, triphenylphosphine, tri-o-tolylphosphine, tricyclohexyl, diphenylphosphineferrocene, in a suitable solvent, such as dimethylformamide, NMP, dichloromethane, tetrahydrofuran, benzene, toluene, pyridine, dimethylsulfoxide at a temperature ranging from - 20°C to reflux, for a suitable time ranging from 15 minutes to 72 hours.

15 According to step b1) of the process, a compound of formula (I) wherein R is -COR', and R₁, R₂, R_a, R_b, R_c, R_d, m and n are as defined above, can be obtained by reacting a compound of formula (I) wherein R is halogen and R₁, R₂, R_a, R_b, R_c, R_d, m and n are as defined above, with a suitable base, such as n-butyl lithium, LDA (lithium diisopropylamide), sec-butyl lithium, t-butyl lithium, lithium 2,2,6,6- 20 tetramethylpiperidin amide, phenyl lithium, magnesium, isopropylmagnesium bromide in a suitable solvent, such as diethyl ether, tetrahydrofuran, 1,4-dioxan, n-hexane, cyclohexane, pentane, toluene, DME (ethylene glycol dimethyl ether), dimethylsulfoxide in the presence of a base if needed, such as TMEDA (N,N,N',N'-tetramethylethylenediamine), at a suitable temperature ranging from -78°C to room 25 temperature, for a time ranging from 15 minutes to 3 hours; the resulting lithium derivative can be quenched with a suitable electrophilic agent, such as, trialkylarylstannane/carbon monoxide, acid chlorides, acid fluorides, acid bromides, anhydrides, carbonates, halo carbonates, carbamates, DMF, and if needed, in the presence of a suitable catalysing agent, such as Pd(0)tetrakis, and of a suitable 30 coordinating agent, such as ZnCl₂, ZnBr₂, CuCN.2LiCl, CuI, CuBr, CuBr.SMe₂ at a

suitable temperature ranging from about -78°C to reflux, for a time ranging from 15 minutes to about 72 hours.

According to step b2) of the process, a compound of formula (I) wherein R is iodine, B(OR'')₂, SnR''', -COOR', -COR', C₁-C₆ alkyl and R₁, R₂, R_a, R_b, R_c, R_d, R', R''', R'''', 5 m and n are as defined above, can be obtained by reacting a compound of formula (I) wherein R is hydrogen and R₁, R₂, R_a, R_b, R_c, R_d, m and n are as defined above, with a suitable lithiating agent, such as n-butyl lithium, LDA, sec-butyl lithium, t-butyl lithium, lithium 2,2,6,6-tetramethylpiperidinamide, phenyl lithium, in a suitable solvent, such as diethyl ether, tetrahydrofuran, 1,4-dioxan, n-hexane, cyclohexane, toluene, DME, 10 dimethylsulfoxide in the presence of a base if needed, such as TMEDA, at a suitable temperature ranging from -78°C to room temperature, for a time ranging from 15 minutes to 3 hours; the resulting lithium derivative can be quenched with a suitable electrophilic agent, such as trialkyl boronic esters, trialkylstannyl chloride, acid chlorides, acid fluorides, acid bromides, anhydrides, carbonates, halo carbonates, DMF, 15 iodine, aldehydes, ketones, alkyl halides, in the presence of a suitable coordinating agent, such as ZnCl₂, ZnBr₂, CuCN.2LiCl, CuI, CuBr, CuBr.SMe₂ when needed, at a suitable temperature ranging from about -78°C to reflux, for a time ranging from 15 minutes to about 72 hours.

According to step c) of the process, a compound of formula (I) wherein R is an 20 optionally substituted aryl or C₁-C₆ alkenyl group and R₁, R₂, R_a, R_b, R_c, R_d, m and n are as defined above, can be obtained by reacting a compound of formula (I) wherein R is B(OR'')₂, SnR''', and R₁, R₂, R_a, R_b, R_c, R_d, R''', R'''', m and n are as defined above, with a suitable aryl halide or halogeno olefine, in the presence of a suitable catalysing 25 agent such as as palladium(0)tetrakis, bis triphenylphosphine palladium(II) dichloride, bis tricyclohexylphosphine palladium(II) dichloride, bis tri-o-tolylphosphine palladium(II) dichloride, palladium(II) acetate, tris(dibenzylideneacetone) dipalladium(0), [1,1'-bis(diphenylphosphino) ferrocene] dichloropalladium(II), [1,1'-bis(diphenylphosphino) ferrocene] dichloronickel(II), 1,4-bis(diphenylphosphino) butane palladium(II), as sodium carbonate, cesium carbonate, potassium carbonate, 30 potassium phosphate, triethylamine, sodium hydroxide, cesium fluoride, potassium tert-butyrate, sodium ethylate, potassium acetate, in a suitable solvent, such as 1,4-dioxan,

tetrahydrofuran, DMF, dimethoxyethane, toluene, methanol, ethanol, water, N-methylpyrrolidone and, if needed, adding a suitable ligand, such as tributylphosphine, triphenylphosphine, tri-*o*-tolylphosphine, tricyclohexyl, biphenyl(dicyclohexyl)phosphine, biphenyl(ditert-butyl)phosphine,

5 diphenylphosphineferrocene, and/or a suitable Cu(I) salts, such as CuI, Cu(I)thiophene-2-carboxylate at a temperature ranging from room temperature to reflux, for a suitable time ranging from 15 minutes to 72 hours.

According to step c) of the process, a compound of formula (I) wherein R is an optionally substituted C₂-C₆ alkynyl, and R₁, R₂, R_a, R_b, R_c, R_d, m and n are as defined above, can be obtained by reacting a compound of formula (I) wherein R is B(OR'')₂, SnR''', and R₁, R₂, R_a, R_b, R_c, R_d, R''', R'''', m and n are as defined above, with a suitable 1-alkyl(aryl)thio-alkyne, 1-iodo(bromo)alkyne, or 1,1-dibromo-1-alkene, in the presence of a suitable catalysing agent such as palladium(0)tetrakis, bis triphenylphosphine palladium(II) dichloride, bis tricyclohexylphosphine palladium(II) dichloride, bis tri-*o*-tolylphosphine palladium(II) dichloride, palladium(II) acetate, tris(dibenzylideneacetone) dipalladium(0), [1,1'-bis(diphenylphosphino) ferrocene] dichloropalladium(II), [1,1'-bis(diphenylphosphino) ferrocene] dichloronickel(II), 1,4-bis(diphenylphosphino) butane palladium(II) in a suitable solvent, such as 1,4-dioxan, tetrahydrofuran, DMF, dimethoxyethane, toluene, methanol, ethanol, water, N-methylpyrrolidone and, if needed, adding a suitable ligand, such as tributylphosphine, triphenylphosphine, tri-*o*-tolylphosphine, tricyclohexyl, biphenyl(dicyclohexyl)phosphine, biphenyl(ditert-butyl)phosphine,

10 diphenylphosphineferrocene, and/or a suitable Cu(I) salts, such as CuI, Cu(I)thiophene-2-carboxylate at a temperature ranging from room temperature to reflux, for a suitable time ranging from 15 minutes to 72 hours.

15 According to step c) of the process, a compound of formula (I) wherein R is an optionally substituted C₂-C₆ alkynyl, and R₁, R₂, R_a, R_b, R_c, R_d, R''', R'''', m and n are as defined above, with a suitable 1-alkyl(aryl)thio-alkyne, 1-iodo(bromo)alkyne, or 1,1-dibromo-1-alkene, in the presence of a suitable catalysing agent such as palladium(0)tetrakis, bis triphenylphosphine palladium(II) dichloride, bis tricyclohexylphosphine palladium(II) dichloride, bis tri-*o*-tolylphosphine palladium(II) dichloride, palladium(II) acetate, tris(dibenzylideneacetone) dipalladium(0), [1,1'-bis(diphenylphosphino) ferrocene] dichloropalladium(II), [1,1'-bis(diphenylphosphino) ferrocene] dichloronickel(II), 1,4-bis(diphenylphosphino) butane palladium(II) in a suitable solvent, such as 1,4-dioxan, tetrahydrofuran, DMF, dimethoxyethane, toluene, methanol, ethanol, water, N-methylpyrrolidone and, if needed, adding a suitable ligand, such as tributylphosphine, triphenylphosphine, tri-*o*-tolylphosphine, tricyclohexyl, biphenyl(dicyclohexyl)phosphine, biphenyl(ditert-butyl)phosphine,

20 diphenylphosphineferrocene, and/or a suitable Cu(I) salts, such as CuI, Cu(I)thiophene-2-carboxylate at a temperature ranging from room temperature to reflux, for a suitable time ranging from 15 minutes to 72 hours.

25 According to steps P and Pa of the process, a compound of formula (III) wherein R, R_a, R_b, R_c, R_d, m and n are as described above, R₁ is as described above but not hydrogen and Q is a solid support can be obtained by reacting a compound of formula (I) wherein R, R_a, R_b, R_c, R_d, m and n are as described above, R₁ is as described above but not hydrogen and R₂ is hydrogen (step P) or different from hydrogen (step Pa), with a suitable solid support such as a polymeric support like isocyanate polystyrenic resin, 2-

chloro-trityl chloride resin, trityl chloride resin, p-nitrophenyl carbonate Wang resin, bromo-4-methoxyphenyl)methyl polystyrene or the like, which are all conventionally known in this field, in the presence, when needed, of a suitable base, such as diisopropylethylamine, triethylamine, 1,8-diazabicyclo[5.4.0] undec-7-ene or 2-tert-
5 butylimino-2-diethylamino-1,3-dimethylperhydro -1,3,2-diaza-phosphorine, in a suitable solvent such as dichloromethane, chloroform, tetrahydrofuran, dimethylformamide, dimethylacetamide, 1-methyl-2-pyrrolidinone, dimethylsulfoxide and the like, at a temperature ranging from room temperature to 50°C, for a suitable time ranging from 10 minutes to 90 hours.

10 According to step b1a) of the process, a compound of formula (I) may be converted into a different compound of formula (I) by steps analogous to the steps b1) herein described for the conversion of a compound of the formula (I) into a different compound of formula (I).

According to step B of the process, a compound of formula (III) may be converted into a
15 different compound of formula (III) by steps analogous to the steps b1), b2), c) and d) herein described for the conversion of a compound of the formula (I) into a different compound of formula (I).

According to step D of the process, a compound of formula (I) wherein R, R_a, R_b, R_c, R_d, m and n are as described above, R₁ is as described above and R₂ is hydrogen, can be
20 obtained by cleaving a compound (III) wherein R, R_a, R_b, R_c, R_d, m and n are as described above, R₁ is as described above and Q is a solid support, according to conventional hydrolytic methods in the presence of a suitable acid, such as hydrochloric acid, acetic acid, trifluoroacetic acid, hydrofluoric acid, or in the presence of a suitable base, such as sodium hydroxide, potassium hydroxide, sodium carbonate, sodium
25 hydrogencarbonate, piperidine, or in the presence of other hydrolytic agents, such as tetrabutyl ammoniumfluoride, trimethyl silylchloride, in a suitable solvent such as dichloromethane, chloroform, methanol, ethanol, trifluoroethanol, dioxan, at a temperature ranging from room temperature to 70°C, for a suitable time ranging from 10 minutes to 90 hours. R₂ is
30 According to step E of the process, a compound of formula (I) wherein R, R_a, R_b, R_c, R_d, m and n are as described above, R₁ is as described above and R₂ is hydrogen may be converted into another different compound of formula (I), the

conversion being carried out in several ways, depending on the meanings of the substituents and the presence of other substituents in the molecule. For example, by this conversion a compound of formula (I) wherein R₂ is as defined above but not hydrogen may be obtained.

5 According to step d) of the process, the conversion of a compound of formula (I) into another different compound of formula (I) may be carried out in several ways, depending on the meanings of the substituents and the presence of other substituents in the molecule. For example, a conversion can be a hydrolysis, a reductive amination, an arylation, an alkylation, an amination, a nucleophilic substitution, a catalytic reduction, an oxidation, 10 a reduction, a condensation with an appropriate reagent or a combination of these reactions.

As an example, the compounds of formula (I) or (III), wherein R₁ is -COO^tBu can be hydrolyzed to the corresponding compounds of formula (I) wherein R₁ is H, by treatment with a suitable acid, for instance trifluoroacetic or hydrochloric acid.

15 So far, any of the above compounds of formula (I) or (III) wherein R₁ is a hydrogen atom can be easily converted into the corresponding derivatives alkylated, acylated, sulfonated or arylated. The reactions are carried out according to conventional techniques, for instance by properly reacting the amino derivative (I) or (III) wherein R₁ is hydrogen with alkylating, acylating, sulfonylating or arylating agents and the like.

20 In particular, a compound of formula (I) or (III) wherein R₁ is selected from R' other than hydrogen, -COR', -COOR', -CONR'R", -SO₂R', or -SO₂NRR", wherein R' and R" have the above reported meanings; R, R₂ and R_a, R_b, R_c, R_d, m and n are as above defined, may be prepared by reacting a compound of formula (I) or a compound of formula (III), having R₁ equal to hydrogen, with a compound of formula (IV)

25 R₁-X (IV)

wherein R₁ is as above defined but not hydrogen and X is a suitable leaving group, preferably fluorine, chlorine, bromine or iodine.

The above reaction can be carried out according to conventional procedures well known in the art for acylating, sulfonylating, alkylating or arylating amino groups, for instance 30 in the presence of a suitable base, such as potassium carbonate, triethylamine, N,N-diisopropylethylamine or pyridine, in a suitable solvent such as dimethylsulfoxide,

toluene, dichloromethane, chloroform, diethyl ether, tetrahydrofuran, acetonitrile, or N,N-dimethylformamide, at a temperature ranging from about -10°C to reflux and for a time varying from about 30 minutes to about 96 hours.

5 A compound of formula (I) or (III) wherein R_1 is an aryl group, R , R_2 and R_a , R_b , R_c , R_d ,
m and n are as above defined, may be prepared by reacting a compound of formula (I) or
a compound of formula (III), having R_1 equal to hydrogen with a compound of formula
(V)

$R_1 \cdot X(V)$

From the foregoing it is clear to the person skilled in the art that the preparation of the compounds of formula (I) or (III) having R_1 equal to $-SO_2NR'R''$ can be actually performed as above described or, alternatively, by properly reacting a compound of formula (I) or (III) having R_1 equal to $-SO_2NHR'$ with any suitable alkylating moiety, according to well known methodologies for preparing di-substituted sulfonamides.

A compound of formula (I) or (III) wherein R₁ is a -CONHR' group, R' has the above reported meanings other than hydrogen, R, R₂, and R_a, R_b, R_c, R_d, m and n are as above defined, may be prepared by reacting a compound of formula (I) or a compound of formula (III) having R₁ equal to hydrogen, with a compound of formula (VI)

5 R'-NCO (VI)

wherein R' is as above defined but not hydrogen, so as to obtain a corresponding compound of formula (I) or (III) which may be optionally further reacted with a compound of formula (VII)

R"-X (VII)

10 wherein R" is as above defined other than hydrogen and X is as above defined, so as to obtain a compound of formula (I) or (III) wherein R₁ is -CONR'R", wherein R' and R" are as above defined but not hydrogen atom.

The reaction between the above compounds (I) or (III) with a compound of formula (VII) can be carried out in the presence of a tertiary base, such as triethylamine, N,N-diisopropylethylamine or pyridine, in a suitable solvent, such as toluene, dichloromethane, chloroform, diethyl ether, tetrahydrofuran, acetonitrile, or N,N-dimethylformamide, at a temperature ranging from about -10°C to reflux and for a time varying from about 30 minutes to about 72 hours.

15 The optional subsequent conversion of a compound of formula (I) or (III) having R₁ equal to -CONHR' into a corresponding derivative having R₁ equal to -CONR'R" is carried out according to conventional methods used to prepare di-substituted ureido derivatives.

20 A compound of formula (I) or (III) wherein R₁ is a -CONR'R" group, R' and R" has the above reported meanings other than hydrogen, R, R₂ and R_a, R_b, R_c, R_d, m and n are as above defined, may be prepared by reacting a compound of formula (I) or a compound of formula (III) having R₁ equal to hydrogen with 4-nitrophenylchloroformate and subsequently with a compound of formula (VIII)

25 R'R"NH (VIII)

wherein R' and R" are as defined above but not hydrogen.

30 The reaction is carried out according to conventional methods used to prepare di-substituted ureido derivatives.

Alternatively, a compound of formula (I) or a compound of formula (III), having R₁ equal to hydrogen may be reacted under reductive conditions with a compound of formula (IX)

R'-CHO (IX)

5 wherein R' is as defined above but not hydrogen, so as to obtain a corresponding compound of formula (I) or (III) wherein R₁ is a -CH₂R' group and R' being as defined above but not hydrogen.

The reaction is carried out in a suitable solvent such as, for instance, N,N-dimethylformamide, N,N-dimethylacetamide, chloroform, dichloromethane, 10 tetrahydrofuran, or acetonitrile, optionally in the presence of acetic acid, ethanol or methanol as co-solvents, at a temperature ranging from about -10°C to reflux and for a time varying from about 30 min to about 4 days.

Conventional reducing agents in the reaction medium are, for instance, sodium boron hydride, sodium triacethoxy boron hydride, and the like.

15 In a further example, any of the above compounds of formula (I) or of formula (III) wherein one or more of R_a, R_b, R_c and R_d is -CH₂OH may be conveniently prepared by starting from a corresponding protected derivative having one or more of R_a, R_b, R_c and R_d as -CH₂-O-Si(Me)₂tBu or -CH₂-O-Ph.

20 The reaction is carried according to conventional techniques, for instance in a suitable solvent such as, for instance, N,N-dimethylformamide, chloroform, dichloromethane, tetrahydrofuran, methanol, ethanol or acetonitrile, at a temperature ranging from about -10°C to reflux and for a time varying from about 30 min to about 72 hours with a suitable fluoride source, for instance tetrabutylammonium fluoride.

25 Likewise, the above compounds of formula (I) or (III) having one or more R_a, R_b, R_c and R_d equal to -CH₂OH can be reacted with a compound of formula (VII')

R'-X (VII')

wherein R' is as above defined but not hydrogen and X is as above defined, so as to obtain the corresponding compounds wherein one or more R_a, R_b, R_c and R_d are a -CH₂OR' group, wherein R' is as defined above but not hydrogen.

30 This latter reaction can be carried out in the presence of a base, such as sodium hydride, N,N-diisopropylethylamine or pyridine, in a suitable solvent, such as toluene,

dichloromethane, chloroform, diethyl ether, tetrahydrofuran, acetonitrile, or N,N-dimethylformamide, at a temperature ranging from about -10°C to reflux.

In an analogous manner, a compound of the formula I wherein R₂ is hydrogen may be converted into another compound of the formula I wherein R₂ is as defined above but 5 not hydrogen atom.

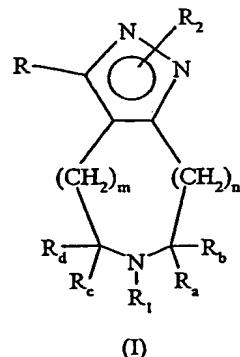
The starting compound of formula (II) are known or can be prepared starting from known compounds using known methods of preparation, for example those described in WO02/12242. As it will be really appreciated by the man skilled in the art, when preparing the compounds of formula (I) object of the invention, optional functional 10 groups within both the starting materials or the intermediates thereof, which could give rise to unwanted side reactions, need to be properly protected according to conventional techniques. Likewise, the conversion of these latter into the free deprotected compounds may be carried out according to known procedures.

The above cited reagents of the process, i.e. arylboronic acids, arylboronic esters, 15 alkenylboronic acids, alkenylboronic esters, triarylstannanes, acid chlorides, acid fluorides, acid bromides, anhydrides, carbonates, halo carbonates, alkynes, aryl halides, halogeno alkenes and the compounds of formula (IV), (V), (VI), (VII), (VII'), (VIII) and (IX) are known or can be prepared according to known methods.

As it will be also really appreciated by the man skilled in the art, when preparing the 20 compounds of formula (I) object of the invention, according to steps a)-c), each of the above cited reactants can be replaced by the corresponding polymer-supported reactant.

In addition to the above, it is also clear to the skilled man that the compounds of formula (I) of the invention can be advantageously prepared by combining the above 25 described reactions in a combinatorial fashion, for example according to solid-phase-synthesis (SPS) techniques, so as to get a combinatorial chemical library of compounds of formula (I).

It is therefore a further object of the invention a library of two or more compounds of formula (I):



wherein R, R₁, R₂, R_a, R_b, R_c, R_d, m and n are as defined above, which can be obtained starting from one or more compound supported onto a solid support of the formula (III) as defined above.

5 PHARMACOLOGY

The compounds of formula (I) are active as protein kinase inhibitors and are therefore useful, for instance, to restrict the unregulated proliferation of tumor cells.

In therapy, they may be used in the treatment of various tumors, such as those formerly reported, as well as in the treatment of other cell proliferative disorders such as 10 psoriasis, vascular smooth cell proliferation associated with atherosclerosis and post-surgical stenosis and restenosis and in the treatment of Alzheimer's disease.

The inhibiting activity of putative cdk/cyclin inhibitors and the potency of selected compounds is determined through a method of assay based on the use of the SPA technology (Amersham Pharmacia Biotech).

15 The assay consists of the transfer of radioactivity labelled phosphate moiety by the kinase to a biotinylated substrate. The resulting 33P-labelled biotinylated product is allowed to bind to streptavidin-coated SPA beads (biotin capacity 130 pmol/mg), and light emitted was measured in a scintillation counter.

Inhibition assay of cdk2/Cyclin A activity

20 **Kinase reaction:** 4 µM in house biotinylated histone H1 (Sigma # H-5505) substrate, 10 µM ATP (0.1 microCi P³³γ-ATP), 1.1 nM Cyclin A/CDK2 complex, inhibitor in a final volume of 30 µl buffer (TRIS HCl 10 mM pH 7.5, MgCl₂ 10 mM, DTT 7.5 mM + 0.2 mg/ml BSA) were added to each well of a 96 U bottom. After incubation for 60 min at room temperature, the reaction was stopped by addition of 100 µl PBS buffer containing 25 32 mM EDTA, 500 µM cold ATP, 0.1% Triton X100 and 10mg/ml streptavidin coated

SPA beads. After 20 min incubation, 110 μ L of suspension were withdrawn and transferred into 96-well OPTIPLATEs containing 100 μ L of 5M CsCl. After 4 hours, the plates were read for 2 min in a Packard TOP-Count radioactivity reader.

IC50 determination: inhibitors were tested at different concentrations ranging from 5 0.0015 to 10 μ M. Experimental data were analyzed by the computer program GraphPad Prizm using the four parameter logistic equation:

$$y = \text{bottom} + (\text{top} - \text{bottom}) / (1 + 10^{((\log IC50 - x) * \text{slope})})$$

where x is the logarithm of the inhibitor concentration, y is the response; y starts at bottom and goes to top with a sigmoid shape.

10 **Ki calculation:**

Experimental method: Reaction was carried out in buffer (10 mM Tris, pH 7.5, 10 mM MgCl₂, 0.2 mg/ml BSA, 7.5 mM DTT) containing 3.7 nM enzyme, histone and ATP (constant ratio of cold/labeled ATP 1/3000). Reaction was stopped with EDTA and the substrate captured on phosphomembrane (Multiscreen 96 well plates from Millipore).

15 After extensive washing, the multiscreen plates were read on a top counter. Control (time zero) for each ATP and histone concentrations was measured.

Experimental design: Reaction velocities are measured at four ATP, substrate (histone) and inhibitor concentrations. An 80-point concentration matrix was designed around the respective ATP and substrate Km values, and the inhibitor IC50 values (0.3, 1, 3, 9 fold 20 the Km or IC50 values). A preliminary time course experiment in the absence of inhibitor and at the different ATP and substrate concentrations allows the selection of a single endpoint time (10 min) in the linear range of the reaction for the Ki determination experiment.

Kinetic parameter estimates: Kinetic parameters were estimated by simultaneous 25 nonlinear least-square regression using [Eq.1] (competitive inhibitor respect to ATP, random mechanism) using the complete data set (80 points):

$$v = \frac{V_m \cdot A \cdot B}{\alpha \cdot K_a \cdot K_b + \alpha \cdot K_a \cdot B + \alpha \cdot K_b \cdot A + A \cdot B + \alpha \cdot \frac{K_a}{K_i} \cdot I \cdot (K_b + \frac{B}{\beta})} \quad [\text{Eq.1}]$$

where A=[ATP], B=[Substrate], I=[inhibitor], V_m= maximum velocity, K_a, K_b, K_i the 30 dissociation constants of ATP, substrate and inhibitor respectively. α and β the

cooperativity factor between substrate and ATP binding and substrate and inhibitor binding respectively.

In addition the selected compounds are characterized on a panel of ser/thre kinases strictly related to cell cycle (cdk2/cyclin E, cdk1/cyclin B1, cdk5/p25, cdk4/ cyclin D1),
5 and also for specificity on MAPK, PKA, EGFR, IGF1-R, Aurora-2 and Cdc 7

Inhibition assay of cdk2/Cyclin E activity

Kinase reaction: 10 μ M in house biotinylated histone H1 (Sigma # H-5505) substrate, 30 μ M ATP (0.3 microCi $P^{33}\gamma$ -ATP), 4 ng GST-Cyclin E/CDK2 complex, inhibitor in a final volume of 30 μ l buffer (TRIS HCl 10 mM pH 7.5, MgCl₂ 10 mM, DTT 7.5 mM +
10 0.2 mg/ml BSA) were added to each well of a 96 U bottom. After incubation for 60 min at room temperature, the reaction was stopped by addition of 100 μ l PBS buffer containing 32 mM EDTA, 500 μ M cold ATP, 0.1% Triton X100 and 10mg/ml streptavidin coated SPA beads. After 20 min incubation, 110 μ L of suspension were withdrawn and transferred into 96-well OPTIPLATEs containing 100 μ l of 5M CsCl.
15 After 4 hours, the plates were read for 2 min in a Packard TOP-Count radioactivity reader.

IC50 determination: see above

Inhibition assay of cdk1/Cyclin B1 activity

Kinase reaction: 4 μ M in house biotinylated histone H1 (Sigma # H-5505) substrate, 20 μ M ATP (0.2 microCi $P^{33}\gamma$ -ATP), 3 ng Cyclin B/CDK1 complex, inhibitor in a final volume of 30 μ l buffer (TRIS HCl 10 mM pH 7.5, MgCl₂ 10 mM, DTT 7.5 mM + 0.2 mg/ml BSA) were added to each well of a 96 U bottom. After 20 min at r.t. incubation, reaction was stopped by 100 μ l PBS + 32 mM EDTA + 0.1% Triton X-100 + 500 μ M ATP, containing 1 mg SPA beads. Then a volume of 110 μ l is transferred to Optiplate.
25 After 20 min. incubation for substrate capture, 100 μ l 5M CsCl were added to allow statification of beads to the top of the Optiplate and let stand 4 hours before radioactivity counting in the Top-Count instrument.

IC50 determination: see above

Inhibition assay of cdk5/p25 activity

30 The inhibition assay of cdk5/p25 activity is performed according to the following protocol.

Kinase reaction: 10 μ M biotinylated histone H1 (Sigma # H-5505) substrate, 30 μ M ATP (0.3 microCi P³³ γ -ATP), 15 ng CDK5/p25 complex, inhibitor in a final volume of 30 μ l buffer (TRIS HCl 10 mM pH 7.5, MgCl₂ 10 mM, DTT 7.5 mM + 0.2 mg/ml BSA) were added to each well of a 96 U bottom. After incubation for 35 min at room temperature, the reaction was stopped by addition of 100 μ l PBS buffer containing 32 mM EDTA, 500 μ M cold ATP, 0.1% Triton X100 and 10mg/ml streptavidin coated SPA beads. After 20 min incubation, 110 μ L of suspension were withdrawn and transferred into 96-well OPTIPLATEs containing 100 μ l of 5M CsCl. After 4 hours, the plates were read for 2 min in a Packard TOP-Count radioactivity reader.

10 **IC50 determination:** see above

Inhibition assay of cdk4/Cyclin D1 activity

Kinase reaction: 0.4 μ M μ M mouse GST-Rb (769-921) (# sc-4112 from Santa Cruz) substrate, 10 μ M ATP (0.5 μ Ci P³³ γ -ATP), 100 ng of baculovirus expressed GST-cdk4/GST-Cyclin D1, suitable concentrations of inhibitor in a final volume of 50 μ l buffer (TRIS HCl 10 mM pH 7.5, MgCl₂ 10 mM, 7.5 mM DTT+ 0.2mg/ml BSA) were added to each well of a 96 U bottom well plate. After 40 min at 37 °C incubation, reaction was stopped by 20 μ l EDTA 120 mM.

Capture: 60 μ l were transferred from each well to MultiScreen plate, to allow substrate binding to phosphocellulose filter. Plates were then washed 3 times with 150 μ l/well PBS Ca⁺⁺/Mg⁺⁺ free and filtered by MultiScreen filtration system.

Detection: filters were allowed to dry at 37°C, then 100 μ l/well scintillant were added and ³³P labeled Rb fragment was detected by radioactivity counting in the Top-Count instrument.

IC50 determination: see above

25 Inhibition assay of MAPK activity

Kinase reaction: 10 μ M in house biotinylated MBP (Sigma # M-1891) substrate, 15 μ M ATP (0.15 microCi P³³ γ -ATP), 30 ng GST-MAPK (Upstate Biotechnology # 14-173), inhibitor in a final volume of 30 μ l buffer (TRIS HCl 10 mM pH 7.5, MgCl₂ 10 mM, DTT 7.5 mM + 0.2 mg/ml BSA) were added to each well of a 96 U bottom. After incubation for 35 min at room temperature, the reaction was stopped by addition of 100 μ l PBS buffer containing 32 mM EDTA, 500 μ M cold ATP, 0.1% Triton X100 and

10mg/ml streptavidin coated SPA beads. After 20 min incubation, 110 μ L of suspension were withdrawn and transferred into 96-well OPTIPLATEs containing 100 μ L of 5M CsCl. After 4 hours, the plates were read for 2 min in a Packard TOP-Count radioactivity reader.

5 **IC50 determination:** see above

Inhibition assay of PKA activity

Kinase reaction: 10 μ M in house biotinylated histone H1 (Sigma # H-5505) substrate, 10 μ M ATP (0.2 microM $P^{33}\gamma$ -ATP), 0.45 U PKA (Sigma # 2645), inhibitor in a final volume of 30 μ L buffer (TRIS HCl 10 mM pH 7.5, MgCl₂ 10 mM, DTT 7.5 mM + 0.2 mg/ml BSA) were added to each well of a 96 U bottom. After incubation for 90 min at room temperature, the reaction was stopped by addition of 100 μ L PBS buffer containing 32 mM EDTA, 500 μ M cold ATP, 0.1% Triton X100 and 10mg/ml streptavidin coated SPA beads. After 20 min incubation, 110 μ L of suspension were withdrawn and transferred into 96-well OPTIPLATEs containing 100 μ L of 5M CsCl. After 4 hours, the plates were read for 2 min in a Packard TOP-Count radioactivity reader.

10 **IC50 determination:** see above

Inhibition assay of EGFR activity

Kinase reaction: 10 μ M in house biotinylated MBP (Sigma # M-1891) substrate, 2 μ M ATP (0.04 microCi $P^{33}\gamma$ -ATP), 36 ng insect cell expressed GST-EGFR, inhibitor in a final volume of 30 μ L buffer (Hepes 50 mM pH 7.5, MgCl₂ 3 mM, MnCl₂ 3 mM, DTT 1 mM, NaVO₃ 3 μ M, + 0.2 mg/ml BSA) were added to each well of a 96 U bottom. After incubation for 20 min at room temperature, the reaction was stopped by addition of 100 μ L PBS buffer containing 32 mM EDTA, 500 μ M cold ATP, 0.1% Triton X100 and 10mg/ml streptavidin coated SPA beads. After 20 min incubation, 110 μ L of suspension were withdrawn and transferred into 96-well OPTIPLATEs containing 100 μ L of 5M CsCl. After 4 hours, the plates were read for 2 min in a Packard TOP-Count radioactivity reader.

15 **IC50 determination:** see above

Inhibition assay of IGF1-R activity

20 The inhibition assay of IGF1-R activity is performed according to the following protocol.

Enzyme activation: IGF1-R must be activated by auto-phosphorylation before starting the experiment. Just prior to the assay, a concentrated enzyme solution (694 nM) is incubated for half a hour at 28°C in the presence of 100 μ M ATP and then brought to the working dilution in the indicated buffer.

5 **Kinase reaction:** 10 μ M biotinylated IRS1 peptide (PRIMM) substrate, 0-20 μ M inhibitor, 6 μ M ATP, 1 microCi 33 P-ATP, and 6 nM GST-IGF1-R (pre-incubated for 30 min at room temperature with cold 60 μ M cold ATP) in a final volume of 30 μ l buffer (50 mM HEPES pH 7.9, 3 mM MnCl₂, 1 mM DTT, 3 μ M NaVO₃) were added to each well of a 96 U bottom well plate. After incubation for 35 min at room temperature, the reaction was stopped by addition of 100 μ l PBS buffer containing 32 mM EDTA, 500 μ M cold ATP, 0.1% Triton X100 and 10mg/ml streptavidin coated SPA beads. After 20 min incubation, 110 μ L of suspension were withdrawn and transferred into 96-well OPTIPLATEs containing 100 μ l of 5M CsCl. After 4 hours, the plates were read for 2 min in a Packard TOP-Count radioactivity reader.

10 **15 Inhibition assay of Aurora-2 activity**

Kinase reaction: 8 μ M biotinylated peptide (4 repeats of LRRWSLG), 10 μ M ATP (0.5 uCi P 33 γ -ATP), 7.5 ng Aurora 2, inhibitor in a final volume of 30 μ l buffer (HEPES 50 mM pH 7.0, MgCl₂ 10 mM, 1 mM DTT, 0.2 mg/ml BSA, 3 μ M orthovanadate) were added to each well of a 96 U bottom well plate. After 60 minutes at room temperature incubation, reaction was stopped and biotinylated peptide captured by adding 100 μ l of bead suspension.

Stratification: 100 μ l of CsCl2 5 M were added to each well and let stand 4 hour before radioactivity was counted in the Top-Count instrument.

IC50 determination: see above

20 **25 Inhibition assay of Cdc7/dbf4 activity**

The inhibition assay of Cdc7/dbf4 activity is performed according to the following protocol.

25 **The Biotin-MCM2 substrate is trans-phosphorylated by the Cdc7/Dbf4 complex in the presence of ATP traced with γ^{33} -ATP. The phosphorylated Biotin-MCM2 substrate is then captured by Streptavidin-coated SPA beads and the extent of phosphorylation evaluated by β counting.**

The inhibition assay of Cdc7/dbf4 activity was performed in 96 wells plate according to the following protocol.

To each well of the plate were added:

- 10 μ l substrate (biotinylated MCM2, 6 μ M final concentration)
- 5 - 10 μ l enzyme (Cdc7/Dbf4, 17.9 nM final concentration)
- 10 μ l test compound (12 increasing concentrations in the nM to μ M range to generate a dose-response curve)
- 10 μ l of a mixture of cold ATP (2 μ M final concentration) and radioactive ATP (1/5000 molar ratio with cold ATP) was then used to start the reaction which was 10 allowed to take place at 37°C.

Substrate, enzyme and ATP were diluted in 50 mM HEPES pH 7.9 containing 15 mM MgCl₂, 2 mM DTT, 3 μ M NaVO₃, 2mM glycerophosphate and 0.2mg/ml BSA. The solvent for test compounds also contained 10% DMSO.

After incubation for 60 minutes, the reaction was stopped by adding to each well 100 μ l 15 of PBS pH 7.4 containing 50 mM EDTA, 1 mM cold ATP, 0.1% Triton X100 and 10 mg/ml streptavidin coated SPA beads.

After 20 min incubation, 110 μ L of suspension were withdrawn and transferred into 96-well OPTIPLATEs containing 100 μ l of 5M CsCl. After 4 hours, the plates were read for 2 min in a Packard TOP-Count radioactivity reader.

20 **IC50 determination:** see above.

The compounds of formula (I) of the present invention, suitable for administration to a mammal, e.g. to humans, can be administered by the usual routes and the dosage level depends upon the age, weight, conditions of the patient and the administration route.

For example, a suitable dosage adopted for oral administration of a compound of 25 formula (I) may range from about 10 to about 500 mg pro dose, from 1 to 5 times daily. The compounds of the invention can be administered in a variety of dosage forms, e.g. orally, in the form of tablets, capsules, sugar or film coated tablets, liquid solutions or suspensions; rectally in the form of suppositories; parenterally, e.g. intramuscularly, or by intravenous and/or intrathecal and/or intraspinal injection or infusion.

30 In addition, the compounds of the invention can be administered either as single agents or, alternatively, in combination with known anticancer treatments such as radiation

therapy or chemotherapy regimen in combination with cytostatic or cytotoxic agents, antibiotic-type agents, alkylating agents, antimetabolite agents, hormonal agents, immunological agents, interferon-type agents, cyclooxygenase inhibitors (e.g. COX-2 inhibitors), metallomatrixprotease inhibitors, telomerase inhibitors, tyrosine kinase inhibitors, anti-growth factor receptor agents, anti-HER agents, anti-EGFR agents, anti-angiogenesis agents, farnesyl transferase inhibitors, ras-raf signal transduction pathway inhibitors, cell cycle inhibitors, other cdk5 inhibitors, tubulin binding agents, topoisomerase I inhibitors, topoisomerase II inhibitors, and the like.

As an example, the compounds of the invention can be administered in combination with one or more chemotherapeutic agents such as, for instance, exemestane, formestane, anastrozole, letrozole, fadrozole, taxane, taxane derivatives, encapsulated taxanes, CPT-11, camptothecin derivatives, anthracycline glycosides, e.g., doxorubicin, idarubicin, epirubicin, etoposide, navelbine, vinblastine, carboplatin, cisplatin, estramustine, celecoxib, tamoxifen, raloxifene, Sugen SU-5416, Sugen SU-6668, Herceptin, and the like, optionally within liposomal formulations thereof.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described above and the other pharmaceutically active agent within the approved dosage range.

Compounds of formula (I) may be used sequentially with known anticancer agents when a combination formulation is inappropriate.

It is therefore a further object of the invention a product or kit comprising the compound of formula (I) of the invention and one or more chemotherapeutic agents for simultaneous, separate or sequential use in anticancer therapy or for the treatment of cell proliferative disorders.

The present invention also includes pharmaceutical compositions comprising an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable excipient, carrier or diluent. The pharmaceutical compositions containing the compounds of the invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable form.

For example, the solid oral forms may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, sucrose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gum, gelatine, 5 methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. a starch, alginic, alginates or sodium starch glycolate; effervescent mixtures; dyestuffs; sweeteners; wetting agents such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in 10 known manner, for example, by means of mixing, granulating, tabletting, sugar-coating, or film-coating processes.

The liquid dispersions for oral administration may be e.g. syrups, emulsions and suspensions.

The syrups may contain as carrier, for example, saccharose or saccharose with glycerine 15 and/or mannitol and/or sorbitol.

The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

The suspension or solutions for intramuscular injections may contain, together with the 20 active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride. The solutions for intravenous injections or infusions may contain as carrier, for example, sterile water or preferably they may be in the form of 25 sterile, aqueous, isotonic saline solutions or they may contain as a carrier propylene glycol.

The suppositories may contain together with the active compound a pharmaceutically acceptable carrier, e.g. cocoa butter, polyethylene glycol, a polyoxyethylene sorbitan fatty ester surfactant or lecithin.

General methods

30 The following examples illustrates the invention without limiting it.

HPLC Conditions

LCMS instrument comprising:

Hewlett Packard 1312A binary pump

Gilson 215 autosampler fitted with a 1ml syringe

Polymer Labs PL1000 Evaporative Light Scattering Detector

5 Micromass ZMD mass spectrometer operating in Electrospray positive ionisation mode.

The LC eluent is split and approximately 200µl/min enters the mass spectrometer, 800µl/min to the ELS. The instruments are currently controlled using Micromass MassLynx 3.5 software under Windows NT4.0

10 HPLC Conditions

Mobile Phase: Aqueous - Water + 0.1% Trifluoroacetic acid
 Organic - Acetonitrile + 0.1% Trifluoroacetic acid

Gradient:	Time (mins)	% Aqueous	% Organic
	0.0	100	0
	1.8	5	95
	2.1	5	95
	2.3	100	0
	2.4	100	0

Run time: 2.4 mins

15 Flow rate: 1 ml/min

Injection vol: 3 µl

Column temperature: ambient (20°C)

Column: 50 x 2.0mm Hypersil C18 BDS; 5µm

ELS Detector Nebuliser Temperature 80oC

20 Evaporation temperature 90oC

Gas Flow 1.5 l/hr

MS Detector m/z 150-800 @ 0.5secs/scan, 0.1second interscan delay

 Cone voltage 25V, Source Temp. 140oC

 Drying Gas 350 l/hr

25 As formerly indicated, several compounds of formula (I) of the invention have been synthesized in parallel, according to combinatorial chemistry techniques.

In this respect, some compounds thus prepared have been conveniently and unambiguously identified, as per the coding system of tables I-III, together with HPLC retention time and mass.

Each code, which identifies a single specific compound of formula (I), consists of three units A-M-B.

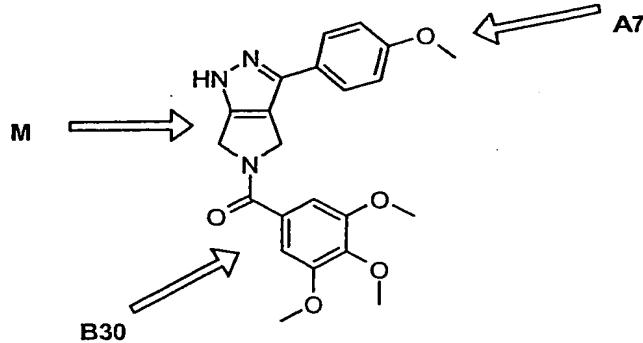
A represents any substituent R- [see formula (I)] and is directly attached to the rest of the pyrrolopyrazole moiety so as to get pyrrolopyrazole derivatives being substituted in position 3 (A-M-B); each A radical (substituent) is represented in the following table I.

B represents any substituent R₁- [see formula (I)] and is attached to the rest of the pyrrolopyrazole moiety through the nitrogen atom so as to get pyrrolopyrazole derivatives being substituted in position 5 (A-M-B); each B radical (substituent) is represented in the following table II.

M refers to the central core of the divalent pyrrolopyrazole moiety and is substituted by groups A and B.

For ease of reference, each A or B groups of tables I and II has been identified with the proper chemical formula also indicating the point of attachment with the rest of the molecule M.

Just as an example, the compound A7-M-B30 of table III (see entry 133) represents a pyrrolopyrazole M being substituted in position 3 (direct bond) by the group A7 and in position 5 (through the -N- group) by the group B30.



entry 133 A7-M-B30

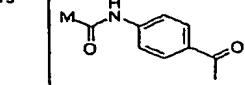
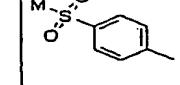
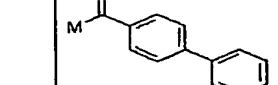
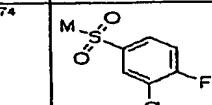
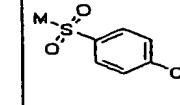
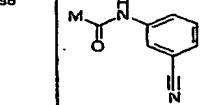
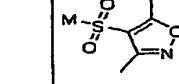
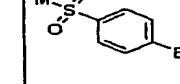
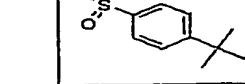
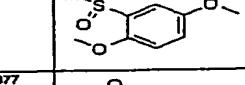
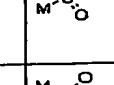
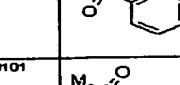
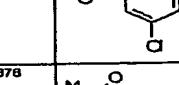
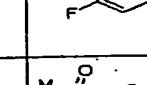
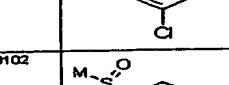
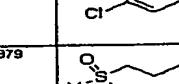
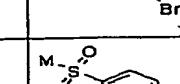
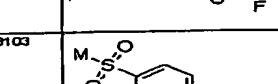
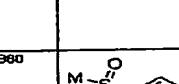
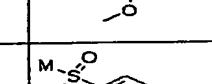
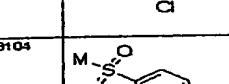
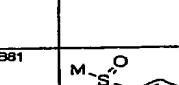
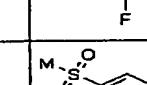
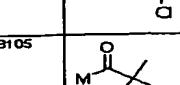
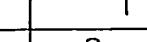
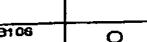
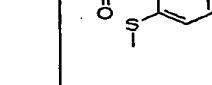
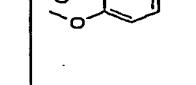
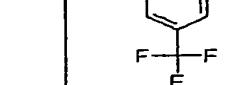
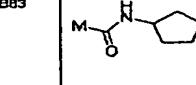
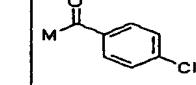
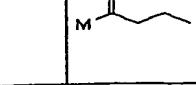
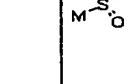
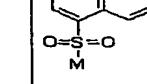
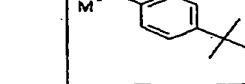
Table I- A group

Code	Fragment	Code	Fragment	Code	Fragment
A1		A11		A21	
A2		A12		A22	
A3		A13		A23	
A4		A14		A24	
A5		A15		A25	
A6		A16		A26	
A7		A17		A27	
A8		A18		A28	
A9		A19		A29	
A10		A20		A30	

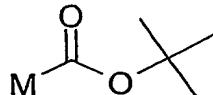
Table II-B groups

Code	Fragment	Code	Fragment	Code	Fragment
B1		B13		B25	
B2		B14		B26	
B3		B15		B27	
B4		B16		B28	
B5		B17		B29	
B6		B18		B30	
B7		B19		B31	
B8		B20		B32	
B9		B21		B33	
B10		B22		B34	
B11		B23		B35	
B12		B24		B36	

Code	Fragment	Code	Fragment	Code	Fragment
B37		B49		B61	
B38		B50		B62	
B39		B51		B63	
B40		B52		B64	
B41		B53		B65	
B42		B54		B66	
B43		B55		B67	
B44		B56		B68	
B45		B57		B69	
B46		B58		B70	
B47		B59		B71	
B48		B60		B72	

Code	Fragment	Code	Fragment	Code	Fragment
B73		B85		B97	
B74		B86		B98	
B75		B87		B99	
B76		B88		B100	
B77		B89		B101	
B78		B90		B102	
B79		B91		B103	
B80		B92		B104	
B81		B93		B105	
B82		B94		B106	
B83		B95		B107	
B84		B96		B108	

Code	Fragment	Code	Fragment	Code	Fragment
B109		B121		B133	
B110		B122		B134	
B111		B123		B135	
B112		B124		B136	
B113		B125		B137	
B114		B126		B138	
B115		B127		B139	
B116		B128		B140	
B117		B129		B141	
B118		B130		B142	
B119		B131		B143	
B120		B132		B144	

Code	Fragment
B145	

Example 1

5 **Preparation of 5-tert-butyloxycarbonyl-1-ethoxycarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (I, R_a=R_b=R_c=R_d= H, R=H, R₁=t-Butyloxycarbonyl(BOC), R₂=ethoxycarbonyl).**

10 A solution of 3-amino-5-tert-butyloxycarbonyl-1-ethoxycarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (0.4g, 1.35 mmol) in dry tetrahydrofuran (10ml) was added drop wise to a solution of isoamyl nitrite (0.32ml, 2.36mmol) in dry tetrahydrofuran (2ml) maintained at reflux. The resulting solution was stirred at reflux for 4 hours, and then cooled to room temperature. After removal of the solvent under vacuum, the crude material was purified by flash chromatography on silica gel using n-hexane:ethyl acetate 90:10; 70:30. The title compound was obtained as a light yellow oil (200mg, y 53%).

15 ¹H-NMR(DMSO-d₆) δ ppm: 7.67(s, 1H); 4.54(m, 2H); 4.39(q,2H); 4.32(m, 2H); 1.43(s,9H); 1.31(t,3H).

Operating in an analogous way, the following compound was also obtained
5-tert-butyloxycarbonyl-2-ethoxycarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole
¹H-NMR(DMSO-d₆) δ ppm: 8.05(s, 1H); 4.39(q,2H); 4.37(m, 4H); 1.43(s,9H); 1.31(t,3H).

Example 2

20 **Preparation of 5-tert-butyloxycarbonyl-1(2)H-4,6-dihydropyrrolo[3,4-c]pyrazole (I, R_a=R_b=R_c=R_d= H, R=H, R₁=t-Butyloxycarbonyl(BOC), R₂= H).**
5-tert-butyloxycarbonyl-1-ethoxycarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (1.5g, 5.3mmol) was treated with a solution of 10% triethylamine in methanol (74 ml) at room temperature for about 20 hours. After removal of the solvents under vacuum, the crude material was dissolved with chloroform (30ml) and washed with water (20mlx2), brine

(20ml), dried over sodium sulphate, filtered and evaporated to dryness. The title compound was obtained as a beige powder (1.08g, yield 97%).

¹H-NMR (DMSO-d₆) δ ppm: 12.63(s,1H); 7.47(s, 1H); 4.31(m, 4H); 1.42(s,9H).

Operating in an analogous way, the following compounds were obtained:

5 **3-iodo-5-t-butyloxycarbonyl-1(2)H-4,6-dihydropyrrolo[3,4-c]pyrazole**

(I, R_a=R_b=R_c=R_d= H, R=I, R₁=t-butyloxycarbonyl, R₂= H)

¹H-NMR (CDCl₃) δ ppm: 11.00 (1H, br. s), 4.60-4.26 (4H, m), 1.46 (9H, s)

3-iodo-5-isopropylaminocarbonyl-1(2)H-4,6-dihydropyrrolo[3,4-c]pyrazole

(I, R_a=R_b=R_c=R_d= H, R=I, R₁=3-isopropylaminocarbonyl, R₂= H).

10 ¹H-NMR (DMSO-d₆) δ ppm: 13.03(s,1H); 5.63(s, 1H); 4.18(m, 4H); 3.78(m, 1H); 1.07(d, 6H).

Example 3

Preparation of 5-tert-butyloxycarbonyl-1-(2-trimethylsilanyl-ethyloxymethyl)-4,6-dihydropyrrolo[3,4-c]pyrazole and 5-tert-butyloxycarbonyl-2-(2-trimethylsilanyl-ethyloxymethyl)-4,6-dihydropyrrolo[3,4-c]pyrazole (I, R_a=R_b=R_c=R_d= H, R=H, R₁=t-Butyloxycarbonyl(BOC), R₂= Trimethylsilanyl-ethoxymethyl (SEM)).

A solution of 5-tert-butyloxycarbonyl-1(2)H-4,6-dihydropyrrolo[3,4-c]pyrazole (0.7g, 3.35mmol) in dry tetrahydrofuran (3ml) was added dropwise to a suspension of 60% sodium hydride (0.147g, 3.68mmol) in dry tetrahydrofuran (2ml), maintained at room temperature under an Argon atmosphere. After 1 hour, the mixture was cooled to 0°C and added with a solution of trimethylsilylethyloxymethyl chloride (SEMCl, 0.651ml, 3.68mmol) in dry tetrahydrofuran (2ml). The reaction mixture was then allowed to warm to room temperature and stirring was continued for about 20 hours. After addition of water (10ml), the mixture was extracted with ethyl acetate (15mlx4). The organic layers were combined, dried over sodium sulphate, filtered and evaporated to dryness under vacuum. The crude material was purified by flash chromatography on silica gel, using cyclohexane:ethyl acetate 80:20 as eluent to yield the title compound (yellow oil, 0.85g, 75% yield) as a mixture of 1-SEM and 2-SEM regioisomers (30:70), which were used without being separated.

30 ¹H-NMR (DMSO-d₆) δ ppm: 7.7(s,1H); 7.32(s,1H); 5.34(s,1H); 5.33(s,1H); 4.4(m, 4H); 4.29(m, 4H); 3.48(m,2X2H); 1.42(s,2X9H); 0.81(m,2X2H); -0.06(m, 2X9H).

Example 4

Preparation of 3-boronic acid-5-tert-butyloxycarbonyl-1-(2-Trimethylsilanyl-ethoxymethyl)- 4,6-dihydropyrrolo[3,4-c]pyrazole and 3-boronic acid-5-tert-butyloxycarbonyl-2-(2-Trimethylsilanyl-ethoxymethyl)- 4,6-dihydropyrrolo[3,4-c]pyrazole (I, R_a=R_b=R_c=R_d= H, R=B(OH)₂, R₁=t-Butyloxycarbonyl(BOC), R₂= Trimethylsilanyl-ethoxymethyl (SEM)).

n-Buthyllithium (1.6M in n-hexane, 0.75ml, 1.2mmol) was slowly added to a solution of the mixture of 5-tert-butyloxycarbonyl-1-(and 2)-(2-Trimethylsilanyl-ethoxymethyl)- 4,6-dihydropyrrolo[3,4-c]pyrazole regioisomers (0.339g, 1mmol) in dry tetrahydrofuran (4ml), maintained under stirring at -78°C, under an argon atmosphere. After 30 minutes, triisopropyl borate (1.15ml, 5mmol) was added dropwise, while keeping the temperature at -78°C. The reaction mixture was allowed to spontaneously warm to room temperature and stirring was continued for about 4.5 hours before quenching with 2N HCl to pH6; water (5ml) was added and the mixture was extracted with ethyl acetate (15mlx4). The organic layers were combined, washed with brine, dried over sodium sulphate, filtered and dried under vacuum to yield the title compound (light orange oil which solidifies on standing, 350mg) as a mixture of 1-SEM and 2-SEM regioisomers, which was used without any further purification.

¹H-NMR (DMSO-d₆) δ ppm: 8.3(m,2H); 7.65(m,2H); 5.54(s,1H); 5.34(s,1H); 4.4-4.3(m, 2X4H); 3.6-3.4(m,2X2H); 1.43(s,2X9H); 0.6(m,2X2H); -0.06- -0.07(m, 2X9H).

Example 5

Preparation of 5-tert-butyloxycarbonyl-3-phenyl-1-(2-trimethylsilanyl-ethoxymethyl)-4,6-dihydropyrrolo[3,4-c]pyrazole (I, R_a=R_b=R_c=R_d= H, R=Ph, R₁=t-Butyloxycarbonyl (BOC), R₂= Trimethylsilanyl-ethoxymethyl (SEM)).

A mixture of 3-boronic acid-5-tert-butyloxycarbonyl-1-(2-Trimethylsilanyl-ethoxymethyl)- 4,6-dihydropyrrolo[3,4-c]pyrazole (70%, 0.060g, 0.16mmol), iodobenzene (0.005 ml, 0.044mmol), sodium carbonate (0.055g, 0.52mmol) and palladium(0)tetrakis (2mg, 5%) in water (0.16ml)-Dimethoxyethane (1ml) was heated under an Argon atmosphere at 80°C for about 6 hours. The mixture was diluted with ethyl acetate (5ml), washed with water (3ml), brine (3ml), dried over sodium sulphate,

filtered and evaporated to dryness. The crude material was purified by flash chromatography to yield the title compound as a light yellow solid (20mg).

Example 6

Preparation of 1-ethoxycarbonyl-5-(3-methylbutanoyl)-3-iodo-4,6-dihydropyrrolo[3,4-c]pyrazole (I, R_a=R_b=R_c=R_d= H, R=Iodo, R₁=3-methylbutanoyl, R₂= 1-ethoxycarbonyl).

5 A solution of 5-tert-butyloxycarbonyl-1-ethoxycarbonyl-3-iodo-4,6-dihydropyrrolo[3,4-c]pyrazole (0.7g, 1.72mmol) in dichloromethane (40ml) was treated with trifluoroacetic acid (9ml) at room temperature for about 4 hours. After removal of the solvents, the 10 crude salt was dissolved with dry tetrahydrofuran (40ml) and added with diisopropyl ethyl amine (1.47ml, 8.6mmol) and isovaleroyl chloride (0.23ml, 1.89ml) diluted with dry tetrahydrofuran (2ml). The reaction mixture was stirred at room temperature for about 20 hours; the solvent was evaporated under vacuum and the crude material was dissolved with dichloromethane (25ml), washed with water (15ml), brine (15ml), dried 15 over sodium sulphate, filtered and dried under vacuum to yield the title compound as a light brown solid which was used without any further purification (0.65g, yield 96%).

1H-NMR (DMSO-d₆) δ ppm: 4.5(m, 2H); 4.38(m, 2H); 4.25(m,2H); 2.18(m,2H) 1.32(m,3H); 0.92(m,6H).

Operating in an analogous way, the following compounds are also obtained:

20 **1-ethoxycarbonyl-3-iodo-5-isopropylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole**

1H-NMR (DMSO-d₆) δ ppm: 6.07(m,1H); 4.59(m, 2H); 4.38(m, 2H); 4.21(m,2H); 3.78(m,1H); 1.32(m,3H); 1.08(m,6H).

Example 7

Preparation of 5-isopropylaminocarbonyl-3-(pyrrol-2-yl)-4,6-dihydropyrrolo[3,4-c]pyrazole (I, R_a=R_b=R_c=R_d= H, R=pyrrol-2-yl, R₁=3-isopropylaminocarbonyl, R₂= H).

25 A mixture of 3-iodo-5-isopropylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (0.15g, 0.38mmol), 1-tert-butyloxycarbonyl-pyrrole-2-boronic acid (0.191g, 0.95mmol), 2M potassium phosphate in water (1ml) and palladium(0)tetrakis (22mg, 5%) in Dimethoxyethane (4ml) was heated under an Argon atmosphere at 80°C for 30 about 7 hours. The mixture was diluted with ethyl acetate (8ml), washed with water (5ml), brine (5ml), dried over sodium sulphate, filtered and evaporated to dryness. The

crude material was purified by flash chromatography, using dichloromethane:methanol 95:5 as eluent to yield the title compound as a light yellow solid (17mg).

¹H-NMR (DMSO-d₆) δ ppm: 6.82-6.10(m,3H); 5.86(d,1H); 4.42(m, 4H); 3.79(m,1H); 1.10(m,6H).

5 Operating in an analogous way, the following compounds were also obtained:
using 2M caesium carbonate as a base:

5-tert-butyloxycarbonyl-3-(1-tert-butyloxycarbonyl-pyrrol-2-yl)-4,6-dihydropyrrolo[3,4-c]pyrazole (I, R_a=R_b=R_c=R_d= H, R=1-tert-butyloxycarbonyl-pyrrol-2-yl, R₁=tert-butyloxycarbonyl, R₂= H).

10 Using sodium carbonate as a base:

5-tert-butyloxycarbonyl-3-(1-tert-butyloxycarbonyl-indol-2-yl)-4,6-dihydropyrrolo[3,4-c]pyrazole (I, R_a=R_b=R_c=R_d= H, R=1-tert-butyloxycarbonyl-indol-2-yl, R₁=tert-butyloxycarbonyl, R₂= H);

3-(1-tert-butyloxycarbonyl-indol-2-yl)-5-(3-methylbutanoyl)-4,6-dihydropyrrolo[3,4-c]pyrazole (I, R_a=R_b=R_c=R_d= H, R=1-tert-butyloxycarbonyl-indol-2-yl, R₁=3-methylbutanoyl, R₂= H).

¹H-NMR (DMSO-d₆) δ ppm: 12.94(s,1H); 7.47(m,4H); 6.91(s,1H); 4.61(m, 4H); 2.18(m,2H); 2.05(m,1H); 1.42(s,9H); 0.91(m,6H).

Using potassium carbonate as a base and a mixture of toluene:ethanol:water 2:1:1 as
20 solvent:

5-tert-butyloxycarbonyl-3-(4-methoxyphenyl)-4,6-dihydropyrrolo[3,4-c]pyrazole
(I, R_a=R_b=R_c=R_d= H, R=4-methoxyphenyl, R₁=t-butoxycarbonyl, R₂= H).

¹H NMR (CDCl₃) δ ppm: 7.4-7.31 (2H, m), 6.95-6.89 (2H, m), 4.50-4.31 (4H, m), 3.78 (3H, br. s), 1.48 (9H, br. s)

25 **Example 8**

Preparation of 3-(indol-2-yl)-5-(3-methylbutanoyl)-4,6-dihydropyrrolo[3,4-c]pyrazole

(I, R_a=R_b=R_c=R_d= H, R=indol-2-yl, R₁=3-methylbutanoyl, R₂= H).

A solution of 3-(1-tert-butyloxycarbonyl-indol-2-yl)-5-(3-methylbutanoyl)-4,6-dihydropyrrolo[3,4-c]pyrazole (0.2g, 0.49mmol) in dichloromethane (3.5ml) was treated
30 with trifluoroacetic acid (0.74ml), at room temperature for about 24 hours. After removal of the solvents under vacuum, the mixture was diluted with dichloromethane

(15ml), washed with saturated sodium bicarbonate, dried over sodium sulphate, filtered and evaporated to dryness. The crude material was purified by flash chromatography, using dichloromethane:methanol 95:5, 90:10 to yield the title compound as beige solid (0.1g, 65%).

5 $^1\text{H-NMR}$ (DMSO-d₆) δ ppm: 13.05(s,1H); 11.22 (bs,1H); 7.47(m,2H); 6.99(m,2H); 6.72(bs,1H); 4.80(m, 4H); 2.27(m,2H); 2.11(m,1H); 0.95(m,6H).

Operating in an analogous way, the following compound was also obtained

3-(1-H-indol-2-yl)-4,6-dihydropyrrolo[3,4-c]pyrazole (I, R_a=R_b=R_c=R_d= H, R=indol-2-yl, R₁=H, R₂= H).

10 $^1\text{H-NMR}$ (DMSO-d₆) δ ppm: 12.71(bs,1H); 11.08 (bs,1H); 6.97(m,2H); 6.72 (s,1H); 6.60(bs,1H); 6.72(bs,1H); 4.07-3.89(m, 4H).

Example 9

Preparation of 5-tert-butyloxycarbonyl-1-ethoxycarbonyl-3-iodo-4,6-dihydropyrrolo[3,4-c]pyrazole (I, R_a=R_b=R_c=R_d= H, R=Iodo, R₁=tert-Butyloxycarbonyl(BOC), R₂= ethoxycarbonyl).

15 Isoamyl nitrite (18.2 ml, 135.2 mmol) was slowly added to a mixture of Iodine (20.58 g, 81.11 mmol) in 145 mL of anhydrous dichloromethane, at +22°C. To this dark mixture a solution of 5-tert-butyloxycarbonyl-1-ethoxycarbonyl-3-amino-4,6-dihydropyrrolo[3,4-c]pyrazole (20.03 g, 67.6 mmol) in 140 mL of dichloromethane was added dropwise over 100 min at +22°C. The internal temperature rose to +28°C and gas evolved during the addition. After 1 hour stirring at room temperature, the reaction mixture was slowly poured in 800ml of 10% sodium metabisulfite. The phases were separated and the aqueous was extracted twice with 300 mL dichloromethane. The combined extracts were dried over anhydrous sodium sulfate and the solvent evaporated under vacuum. This raw material was purified by flash chromatography eluting with 20:80 EtOAc/cyclohexane. A light yellow product (25.5 g) was obtained which was finally purified with MTBE (60 mL) and n-hexane (60 mL): 21.8 g of high purity, white product was isolated (79% yield). m.p. 166-168°C.

20 $^1\text{H-NMR}$ (DMSO-d₆) δ ppm: 4.58(m, 2H); 4.38(q,2H); 4.24(m, 2H); 1.43(s,9H); 1.32(t,3H).

Example 10

Preparation of 5-tert-butyloxycarbonyl-3-iodo-4,6-dihydropyrrolo[3,4-c]pyrazole

(I, R_a=R_b=R_c=R_d= H, R=Iodo, R₁=t-Butyloxycarbonyl(BOC), R₂= H).

1-ethoxycarbonyl-3-iodo-5-tert-butyloxycarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole

1-ethoxycarbonyl-3-iodo-5-tert-butyloxycarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (270 mg, 0.66 mmol) was stirred with a mixture of MeOH (2 ml) and triethylamine (0.5 ml) at room temperature for about 30 min.

5 The solvents were evaporated and the compound was dried under vacuum. White solid (220 mg).

Example 11**Preparation of 5-tert-butyloxycarbonyl-3-phenyl-4,6-dihydropyrrolo[3,4-**

c]pyrazole (I, R_a=R_b=R_c=R_d= H, R=Phenyl, R₁=t-Butyloxycarbonyl(BOC), R₂= H).

10 A mixture of 5-tert-butyloxycarbonyl-1-ethoxycarbonyl-3-iodo-4,6-dihydropyrrolo[3,4-c]pyrazole (60 mg, 0.15mmol), phenylboronic acid (22 mg, 0,18mmol), potassium carbonate (31 mg, 0.22 mmol), triethylamine (ml 0.03, 0.22 mmol) and palladium dichloride-diphenylphosphine (8mg, 7%) in dioxan/water 10/1 (2ml) was heated under Argon atmosphere at 80°C for about 3 hours. The mixture was diluted with ethyl acetate (8ml), washed with water (5ml), brine (5ml), dried over sodium sulphate, filtered and evaporated to dryness. The crude material was purified by flash chromatography, using Ethylacetate/hexane as eluent to yield the title compound as a light yellow solid (27mg 63%).

Example 12**Preparation of 5-acetyl-3-phenyl-4,6-dihydropyrrolo[3,4-c]pyrazole (I,**

R_a=R_b=R_c=R_d= H, R=Phenyl, R₁=Acetyl, R₂= H).

A solution of 5-tert-butyloxycarbonyl-3-phenyl-4,6-dihydropyrrolo[3,4-c]pyrazole

25 (90 mg, 0.31 mmol) in dichloromethane (3.5ml) was treated with trifluoroacetic acid (0.5ml), at room temperature for about 4 hours. After removal of the solvents, the crude salt was dissolved with dry dichloromethane (5ml) and diisopropylethylamine (0.32 ml, 1.86mmol) and acetyl chloride (0.07ml, 0.9 mmol) were added. The reaction mixture was stirred at room temperature for about 2 hours; the crude material was diluted with dichloromethane (25ml), washed with water (15ml), brine (15ml), dried over sodium sulphate, filtered and dried under vacuum. The crude was suspended in a solution of

sodium bicarbonate and stirred at room temperature for about 3 hours, then extracted with ethylacetate to yield the title compound as a light brown solid (40 mg).

Example 13

Preparation of 5-tert-butyloxycarbonyl-3-iodo-1-polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (III, R_a=R_b=R_c=R_d= H, R=Iodo, R₁=t-Butyloxycarbonyl(BOC), Q= polystyrenemethylaminocarbonyl).

The isocyanate methylpolystyrene resin (1.14 g, 1.71 mmol) was swelled with 15 ml of dichloromethane, and a solution of 5-tert-butyloxycarbonyl-3-iodo-4,6-dihydropyrrolo[3,4-c]pyrazole (410 mg, 1.22 mmol) in 3 ml of dimethylformamide was added.

The mixture was stirred at room temperature for about 24 hours; after filtration, the resin was washed with dichloromethane (2 x 20 ml), MeOH (2 x 20 ml), dimethylformamide (2 x 20 ml) and dichloromethane (3 x 20 ml).

15 The resin was dried under vacuum.

Operating in an analogous way, the following compound was also obtained
5-tert-butyloxycarbonyl-3-(4-methoxyphenyl)-1-polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (III, R_a=R_b=R_c=R_d= H, R=4-methoxyphenyl, R₁=t-Butyloxycarbonyl(BOC), Q= polystyrenemethylaminocarbonyl).

20 **Example 14**

Preparation of

5-tert-butyloxycarbonyl-3-phenyl-1-polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (III, R_a=R_b=R_c=R_d= H, R=Phenyl, R₁=t-Butyloxycarbonyl(BOC), Q= polystyrenemethylaminocarbonyl).

25 To a suspension of 5-tert-butyloxycarbonyl-3-iodo-1-polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (117 mg, 0.17 mmol) in dioxan/water 10/1 (3 ml), phenylboronic acid (108 mg, 0.88 mmol), potassium carbonate (171 mg, 0.8 mmol), triethylamine (0.18 ml, 0.8 mmol) and palladium dichloride diphenylphosphine (25 mg, 20%) were added.

The mixture was stirred at 80°C for about 8 hours; after filtration, the resin was washed with dichloromethane (2 x 20 ml), MeOH (2 x 20 ml), dimethylformamide (2 x 20 ml) and dichloromethane (3 x 20 ml).

The resin was dried under vacuum.

5 Operating in an analogous way, using a suitable boronic acid, the following compounds were also obtained:

5-tert-butyloxycarbonyl-3-(4-phenoxy-phenyl)-1-

polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (III,
R_a=R_b=R_c=R_d= H, R=4-phenoxy-phenyl, R₁=t-Butyloxycarbonyl(BOC), Q=

10 polystyrenemethylaminocarbonyl);

3-(4-benzyloxy-phenyl)-5-tert-butyloxycarbonyl-1-

polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (III,
R_a=R_b=R_c=R_d= H, R=4-benzyloxy-phenyl, R₁=t-Butyloxycarbonyl(BOC), Q=

polystyrenemethylaminocarbonyl);

15 5-tert-butyloxycarbonyl-3-(5-chloro-thiophen-2-yl)-1-

polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (III,
R_a=R_b=R_c=R_d= H, R=5-chloro-thiophen-2-yl, R₁=t-Butyloxycarbonyl(BOC), Q=

polystyrenemethylaminocarbonyl);

20 5-tert-butyloxycarbonyl-3-(4-methoxy-phenyl)-1-

polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (III,
R_a=R_b=R_c=R_d= H, R=4-methoxy-phenyl, R₁=

t-Butyloxycarbonyl(BOC), Q= polystyrenemethylaminocarbonyl) and

25 5-tert-butyloxycarbonyl-3-(4-dimethylamino-phenyl)-1-

polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (III,
R_a=R_b=R_c=R_d= H, R=4-dimethylamino-phenyl, R₁=t-Butyloxycarbonyl(BOC), Q=

polystyrenemethylaminocarbonyl).

Example 15

Preparation of

30 5-tert-butyloxycarbonyl-3-phenylethynyl-1-polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (III, R_a=R_b=R_c=R_d= H, R=Phenylethynyl, R₁=t-Butyloxycarbonyl(BOC), Q= polystyrenemethylaminocarbonyl).

To a suspension of 5-tert-butyloxycarbonyl-3-iodo-1-polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (200 mg, 0.21 mmol) in dioxan (2 ml), phenylethyne (0.23 ml, 2 mmol), CuI (20 mg, 50%), triethylamine (0.12 ml, 1.5 mmol) and palladium dichloride diphenylphosphine (29 mg, 20%) were added.

5 The mixture was stirred at 80°C for about 8 hours; after filtration, the resin was washed with dichloromethane (2 x 20 ml), MeOH (2 x 20 ml), dimethylformamide (2 x 20 ml) and with dichloromethane (3 x 20 ml).

The resin was dried under vacuum.

Example 16

10 **Preparation of 3-phenyl-1-polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (III, R_a=R_b=R_c=R_d= H, R=Phenyl, R₁=H, Q= polystyrenemethylaminocarbonyl).**

To 5-tert-butyloxycarbonyl-3-phenyl-1-polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole swelled in dichloromethane (5 ml) trifluoroacetic acid (1 ml) was added.

The mixture was stirred at room temperature for about 4 hours, after filtration, the resin was washed with dichloromethane (2 x 20 ml), MeOH (2 x 20 ml), dimethylformamide (2 x 20 ml) and dichloromethane (3 x 20 ml).

The resin was dried under vacuum.

20 Operating in an analogous way, the following compounds were also obtained:

3-(4-phenoxy-phenyl)-1-polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (III, R_a=R_b=R_c=R_d= H, R=Phenyl, R₁=H, Q= polystyrenemethylaminocarbonyl);

3-(4-benzyloxy-phenyl)-1-polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (III, R_a=R_b=R_c=R_d= H, R=4-Benzylxyphenyl, R₁=H, Q= polystyrenemethylaminocarbonyl);

3-(5-chloro-thiophen-2-yl)-1-polystyrenemethylaminocarbonyl-4,6-dihydro-pyrrolo[3,4-c]pyrazole (III, R_a=R_b=R_c=R_d= H, R=5-Chloro-thiophen-2-yl, R₁=H, Q= polystyrenemethylaminocarbonyl);

3-(4-methoxy-phenyl)-1-polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (III, $R_a=R_b=R_c=R_d=H$, $R=4$ -Methoxyphenyl, $R_1=H$, $Q=$ polystyrenemethylaminocarbonyl);

5 3-(4-dimethylamino-phenyl)-1-polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (III, $R_a=R_b=R_c=R_d=H$, $R=4$ -Dimethylaminophenyl, $R_1=H$, $Q=$ polystyrenemethylaminocarbonyl);

10 3-phenylethynyl-1-polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (III, $R_a=R_b=R_c=R_d=H$, $R=$ Phenylethynyl, $R_1=H$, $Q=$ polystyrenemethylaminocarbonyl) and

15 3-(4-methoxyphenyl)-1-polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (III, $R_a=R_b=R_c=R_d=H$, $R=4$ -methoxyphenyl, $R_1=H$, $Q=$ polystyrenemethylaminocarbonyl).

Example 17

Preparation of 5-acetyl-3-phenyl-1-polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (III, $R_a=R_b=R_c=R_d=H$; $R=$ Phenyl, $R_1=$ Acetyl, $Q=$ polystyrenemethylaminocarbonyl).

To 3-phenyl-1-polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole swelled in dichloromethane (5 ml) diisopropylethylamine (0.21 ml, 1.24 mmol) and acetylchloride (0.06 ml. 0.88 mmol) were added.

20 The mixture was stirred at room temperature for about 24 hours; after filtration, the resin was washed with dichloromethane (2 x 20 ml), MeOH (2 x 20 ml), dimethylformamide (2 x 20 ml) and dichloromethane (3 x 20 ml). The resin was dried under vacuum.

Operating in an analogous way, the following compounds were also obtained:

25 5-acetyl-3-(4-phenoxy-phenyl)-1-polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (III, $R_a=R_b=R_c=R_d=H$, $R=4$ -Phenoxyphenyl, $R_1=$ Acetyl, $Q=$ polystyrenemethylaminocarbonyl);

5-acetyl-3-(4-benzyloxy-phenyl)-1-polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (III, $R_a=R_b=R_c=R_d=H$, $R=4$ -Benzylxyphenyl, $R_1=$ Acetyl, $Q=$ polystyrenemethylaminocarbonyl);

30

5-acetyl-3-(5-chloro-thiophen-2-yl)-1-polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (III, $R_a=R_b=R_c=R_d=H$, $R=5$ -Chloro-thiophen-2-yl, $R_1=$ Acetyl, $Q=$ polystyrenemethylaminocarbonyl);

5-acetyl-3-(4-methoxy-phenyl)-1-polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (III, $R_a=R_b=R_c=R_d=H$, $R=4$ -Methoxyoxyphenyl, $R_1=$ Acetyl, $Q=$ polystyrenemethylaminocarbonyl);

5-acetyl-3-(4-dimethylamino-phenyl)-1-polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (III, $R_a=R_b=R_c=R_d=H$, $R=4$ -Dimethylamino-phenyl, $R_1=$ Acetyl, $Q=$ polystyrenemethylaminocarbonyl);

5-acetyl-3-phenylethynyl-1-polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (III, $R_a=R_b=R_c=R_d=H$, $R=$ Phenylethynyl, $R_1=$ Acetyl, $Q=$ polystyrenemethylaminocarbonyl) and

3-(4-t-butylphenyl)-5-(2-phenoxypropionyl)-1-polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (III, $R_a=R_b=R_c=R_d=H$, $R=4$ -t-butylphenyl, $R_1=2$ -phenoxypropionyl, $Q=$ polystyrenemethylaminocarbonyl).

Example 18

Preparation of 5-isopropylaminocarbonyl-3-phenyl-1-polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (III, $R_a=R_b=R_c=R_d=H$, $R=$ Phenyl, $R_1=$ Isopropylaminocarbonyl, $Q=$ polystyrenemethylaminocarbonyl).

To 3-phenyl-1-polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole swelled in dichloromethane (5 ml) isopropylisocyanate (0.09 ml. 0.88 mmol) was added. The mixture was stirred at room temperature for about 24 hours; after filtration, the resin was washed with dichloromethane (2 x 20 ml), MeOH (2 x 20 ml), dimethylformamide (2 x 20 ml) and dichloromethane (3 x 20 ml). The resin was dried under vacuum.

Operating in an analogous way, the following compounds were also obtained:

5-isopropylaminocarbonyl-3-(4-phenoxy-phenyl)-1-polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (III, $R_a=R_b=R_c=R_d=H$, $R=4$ -Phenoxyphenyl, $R_1=$ Isopropylaminocarbonyl, $Q=$ polystyrenemethylaminocarbonyl);

3-(4-benzyloxy-phenyl)-5-isopropylaminocarbonyl-1-
 polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole
 (III, R_a=R_b=R_c=R_d= H, R=4-Benzyloxyphenyl, R₁=Isopropylaminocarbonyl,
 Q= polystyrenemethylaminocarbonyl);

5 3-(5-chloro-thiophen-2-yl)-5-isopropylaminocarbonyl -1-
 polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole
 (III, R_a=R_b=R_c=R_d= H, R=5-Chloro-thiophen-2-yl, R₁=Isopropylaminocarbonyl,
 Q= polystyrenemethylaminocarbonyl);

10 5-isopropylaminocarbonyl -3-(4-methoxy-phenyl)- 1-polystyrenemethylamino
 carbonyl-4,6-dihydro-pyrrolo[3,4-c]pyrazole
 (III, R_a=R_b=R_c=R_d= H, R=4-Methoxy-phenyl, R₁=Isopropylaminocarbonyl,
 Q= polystyrenemethylaminocarbonyl);

15 3-(4-dimethylamino-phenyl)-5-isopropylaminocarbonyl -1-
 polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole
 (III, R_a=R_b=R_c=R_d= H, R=4-Dimethylamino-phenyl, R₁=Isopropylaminocarbonyl,
 Q= polystyrenemethylaminocarbonyl);

20 5-isopropylaminocarbonyl -3-phenylethynyl- 1-polystyrenemethylaminocarbonyl-
 4,6-dihydropyrrolo[3,4-c]pyrazole (III, R_a=R_b=R_c=R_d= H, R=Phenylethynyl,
 R₁=Isopropylaminocarbonyl, Q= polystyrenemethylaminocarbonyl) and

25 3-(2,5-dimethylphenyl)-5-n-propylaminocarbonyl-1-
 polystyrenemethylaminocarbonyl -4,6-dihydropyrrolo[3,4-c]pyrazole (III,
 R_a=R_b=R_c=R_d= H, R=4-(2,5-dimethylphenyl), R₁=n-propylaminocarbonyl, Q= polystyrenemethylaminocarbonyl).

Example 19

25 Preparation of 5-acetyl-3-phenyl-4,6-dihydropyrrolo[3,4-c]pyrazole
 (R_a=R_b=R_c=R_d= H, R=Phenyl, R₁=Acetyl, R₂= H).
 To 5-acetyl-3-phenyl-1-polystyrenemethylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (200 mg) swelled in dioxan (3 ml), sodium hydroxide (35% in water) was added (0.4 ml) and the mixture was stirred at 40°C for about 90 hours.

30 After neutralization of the solution, the mixture was filtered and the desired product was dried under vacuum: a white solid (40 mg) was obtained.

Operating in an analogous way, the following compounds were also obtained.

5-Isopropylaminocarbonyl-3-phenyl-4,6-dihydropyrrolo[3,4-c]pyrazole

(R_a=R_b=R_c=R_d= H, R=Phenyl, R₁=Isopropylaminocarbonyl, R₂= H).

¹H-NMR (DMSO-d₆) δ ppm: 13.12 (s,1H); 7.58-7.32(m,5H); 5.97(d,1H); 4.53(m, 4H);

5 3.38(m,1H); 1.10(m,6H);

5-Acetyl-3-(4-phenoxy-phenyl)- 4,6-dihydropyrrolo[3,4-c]pyrazole (R_a=R_b=R_c=R_d=

H, R=4-Phenoxy-phenyl, R₁=Acetyl, R₂= H).

¹H-NMR (DMSO-d₆) δ ppm: 13.11(s,1H); 7.62-7.05(m,9H); 4.78(m, 4H); 2.06(s,3H).

5-Isopropylaminocarbonyl-3-(4-phenoxy-phenyl)- 4,6-dihydropyrrolo[3,4-

10 **c]pyrazole (R_a=R_b=R_c=R_d= H, R=4-Phenoxy-phenyl , R₁=Isopropylaminocarbonyl, R₂= H).**

¹H-NMR (DMSO-d₆) δ ppm: 13.06 (s,1H); 7.59-7.04(m,9H); 5.93(d,1H); 4.51-4.42(m, 4H); 3.80(m,1H); 1.09(m,6H).

5-Acetyl-3-(4-benzyloxy-phenyl)- 4,6-dihydropyrrolo[3,4-c]pyrazole

15 (R_a=R_b=R_c=R_d= H, R=4-Benzyloxy-phenyl, R₁=Acetyl, R₂= H):

3-(4-benzyloxy-phenyl)-5-isopropylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (R_a=R_b=R_c=R_d= H, R=4-Benzyloxy-phenyl , R₁=Isopropylaminocarbonyl, R₂= H).

5-Acetyl-3-(5-chloro-thiophen-2-yl)- 4,6-dihydropyrrolo[3,4-c]pyrazole

20 (R_a=R_b=R_c=R_d= H, R=5-Chloro-thiophen-2-yl, R₁=Acetyl, R₂= H).

¹H-NMR (DMSO-d₆) δ ppm: 13.07(s,1H); 7.14(m,2H); 4.69(m, 4H); 2.04(s,3H).

3-(5-Chloro-thiophen-2-yl)-5-isopropylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole (R_a=R_b=R_c=R_d= H, R=5-Chloro-thiophen-2-yl, R₁=Isopropylaminocarbonyl, R₂= H).

25 ¹H-NMR (DMSO-d₆) δ ppm: 13.13(s,1H); 7.14(m,2H); 5.94(d,1H); 4.41(m, 4H); 3.79(m,1H); 1.10(m,6H).

5-Acetyl-3-(4-methoxy-phenyl)- 4,6-dihydropyrrolo[3,4-c]pyrazole (R_a=R_b=R_c=R_d=

H, R=4-Methoxy-phenyl, R₁=Acetyl, R₂= H);

5-isopropylaminocarbonyl-3-(4-methoxy-phenyl)- 4,6-dihydropyrrolo[3,4-

30 **c]pyrazole (R_a=R_b=R_c=R_d= H, R=4-Methoxy-phenyl, R₁= Isopropylaminocarbonyl, R₂= H);**

5-acetyl-3-(4-dimethylamino-phenyl)- 4,6-dihydropyrrolo[3,4-c]pyrazole(R_a=R_b=R_c=R_d= H, R=4-Dimethylamino-phenyl, R₁=Acetyl, R₂= H).¹H-NMR (DMSO-d₆) δ ppm: 7.44-7.41(dd,2H); 6.75-6.77(d,2H); 4.74-4.21(m, 4H); 2.87(s,6H); 2.00(s,3H).

5 **3-(4-Dimethylamino-phenyl)-5-isopropylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole** (R_a=R_b=R_c=R_d= H, R=4-Dimethylamino-phenyl, R₁=Isopropylaminocarbonyl, R₂= H).

¹H-NMR (DMSO-d₆) δ ppm: 7.40(m,2H); 6.77(m,2H); 4.18(m, 4H); 3.78(m,1H); 2.92 (s,6H); 1.11(m,6H).

10 **5-Acetyl-3-phenylethynyl-4,6-dihydropyrrolo[3,4-c]pyrazole** (R_a=R_b=R_c=R_d=H, R=Phenylethynyl, R₁=Acetyl, R₂= H).

¹H-NMR (DMSO-d₆) δ ppm: 7.53-7.42(m,5H); 4.35(m, 4H); 3.80(m,1H); 1.03 (m,6H).**5-Isopropylaminocarbonyl-3-phenylethynyl-4,6-dihydropyrrolo[3,4-c]pyrazole**(R_a=R_b=R_c=R_d= H, R=Phenylethynyl, R₁= Isopropylaminocarbonyl, R₂= H)

15 **3-(2,5-dimethylphenyl)-5-n-propylaminocarbonyl-4,6-dihydropyrrolo[3,4-c]pyrazole**

(I, R_a=R_b=R_c=R_d= H, R=4-(2,5-dimethylphenyl), R₁=n-propylaminocarbonyl, R₂=H).LCMS: *m/z* 299 [M+H]⁺ @ R_T 1.21 min (81% by ELS detection).**3-(4-t-butylphenyl)-5-(2-phenoxypropionyl)-4,6-dihydropyrrolo[3,4-c]pyrazole** (I,20 R_a=R_b=R_c=R_d= H, R=4-t-butylphenyl, R₁=2-phenoxypropionyl, R₂=H).¹H NMR (DMSO-d₆) δ ppm: 7.61-7.53 (2H, m), 7.52-7.45 (2H, m), 7.30-7.22 (2H, m), 6.96-6.87 (3H, m), 5.22-5.12 (1H, m), 4.97-4.84 (1H, m), 4.72-4.62 (2H, m), 4.51-4.47 (1H, m), 1.60-1.50 (3H, m), 1.32 (9H, br. S), pyrazole NH not observed;LCMS: *m/z* 390 [M+H]⁺ @ R_T 1.57 min (88% by ELS detection).

25 By proceeding in the same way as described in examples 7, 13, 16, 17, 18 and 19, 1048 products were synthesized in parallel and coded in table III, as formerly indicated; related HPLC retention time together with experimentally found [M+H]⁺ are reported.

Tabella III

Entry	Compound	r.t (min)	[M+H] ⁺
1	A1-M-B1	1.24	304.1
2	A2-M-B1	1.26	304.1
3	A3-M-B1	1.1	280.1
4	A4-M-B1	1.22	350.1
5	A5-M-B1	1.24	310.1
6	A1-M-B2	1.3	318.2
7	A2-M-B2	1.33	318.2
8	A5-M-B2	1.31	324.1
9	A1-M-B3	1.38	310.2
10	A2-M-B3	1.4	310.2
11	A6-M-B3	1.29	302.1
12	A3-M-B3	1.24	286.1
13	A4-M-B3	1.35	356.2
14	A5-M-B3	1.38	316.1
15	A1-M-B4	1.02	242.1
16	A2-M-B4	1.06	242.1
17	A7-M-B4	0.98	258.1
18	A3-M-B4	0.88	218.1
19	A1-M-B5	1.5	324.2
20	A8-M-B5	1.48	370.2
21	A3-M-B5	1.37	300.2
22	A5-M-B5	1.52	330.2
23	A1-M-B6	1.35	338.1
24	A2-M-B6	1.37	338.1
25	A6-M-B6	1.27	330.0
26	A8-M-B6	1.34	384.1
27	A3-M-B6	1.22	314.1
28	A5-M-B6	1.36	344.1
29	A1-M-B7	1.29	348.2
30	A9-M-B7	1.32	348.2
31	A2-M-B7	1.32	348.2
32	A3-M-B7	1.17	324.1
33	A4-M-B7	1.27	394.2
34	A1-M-B8	1.24	348.1
35	A9-M-B8	1.26	348.1
36	A2-M-B8	1.26	348.1
37	A8-M-B8	1.22	394.1
38	A3-M-B8	1.1	324.1
39	A5-M-B8	1.24	354.1
40	A1-M-B9	1.31	334.1
41	A3-M-B9	1.2	310.1
42	A4-M-B9	1.3	380.2
43	A1-M-B10	1.36	298.2
44	A8-M-B10	1.34	344.2
45	A3-M-B10	1.23	274.1
46	A5-M-B10	1.37	304.1

Entry	Compound	r.t (min)	[M+H] ⁺
47	A1-M-B11	1.27	322.1
48	A9-M-B11	1.3	322.1
49	A2-M-B11	1.3	322.1
50	A6-M-B11	1.2	314.1
51	A8-M-B11	1.27	368.1
52	A3-M-B11	1.15	298.1
53	A5-M-B11	1.28	328.1
54	A9-M-B12	1.27	339.1
55	A1-M-B13	1.24	310.1
56	A3-M-B13	1.11	286.1
57	A5-M-B13	1.25	316.1
58	A1-M-B14	1.18	364.2
59	A2-M-B14	1.21	364.2
60	A6-M-B14	1.11	356.1
61	A3-M-B14	1.06	340.1
62	A5-M-B14	1.18	370.1
63	A1-M-B15	1.14	268.1
64	A3-M-B15	1.01	244.1
65	A5-M-B15	1.17	274.1
66	A1-M-B16	1.25	334.1
67	A9-M-B16	1.28	334.1
68	A2-M-B16	1.28	334.1
69	A3-M-B16	1.13	310.1
70	A5-M-B16	1.25	340.1
71	A1-M-B17	1.2	256.1
72	A4-M-B17	1.12	302.1
73	A1-M-B18	1.33	340.1
74	A6-M-B18	1.26	332.1
75	A8-M-B18	1.32	386.1
76	A3-M-B18	1.21	316.1
77	A5-M-B18	1.33	346.1
78	A1-M-B19	1.25	334.1
79	A9-M-B19	1.27	334.1
80	A2-M-B19	1.27	334.1
81	A6-M-B19	1.17	326.1
82	A3-M-B19	1.12	310.1
83	A5-M-B19	1.25	340.1
84	A1-M-B20	1.14	323.1
85	A9-M-B20	1.18	323.1
86	A2-M-B20	1.17	323.1
87	A6-M-B20	1.07	315.1
88	A8-M-B20	1.14	369.1
89	A7-M-B20	1.1	339.1
90	A3-M-B20	1.01	299.1
91	A5-M-B20	1.15	329.1
92	A1-M-B21	1.27	322.1

Entry	Compound	r.t (min)	[M+H] ⁺
93	A9-M-B21	1.29	322.1
94	A2-M-B21	1.29	322.1
95	A6-M-B21	1.19	314.1
96	A8-M-B21	1.25	368.1
97	A7-M-B21	1.21	338.1
98	A3-M-B21	1.14	298.1
99	A5-M-B21	1.3	328.1
100	A1-M-B22	1.32	296.2
101	A9-M-B22	1.38	296.2
102	A2-M-B22	1.35	296.2
103	A6-M-B22	1.23	288.1
104	A8-M-B22	1.31	342.2
105	A3-M-B22	1.18	272.1
106	A5-M-B22	1.32	302.1
107	A1-M-B23	1.36	332.2
108	A8-M-B23	1.35	378.2
109	A3-M-B23	1.25	308.1
110	A1-M-B24	1.34	348.2
111	A9-M-B24	1.37	348.2
112	A7-M-B24	1.29	364.2
113	A3-M-B24	1.22	324.1
114	A1-M-B25	1.32	338.1
115	A9-M-B25	1.33	338.1
116	A2-M-B25	1.33	338.1
117	A8-M-B25	1.29	384.1
118	A7-M-B25	1.25	354.1
119	A3-M-B25	1.18	314.1
120	A8-M-B26	1.22	375.1
121	A1-M-B27	1.24	282.2
122	A2-M-B27	1.28	282.2
123	A3-M-B27	1.11	258.1
124	A1-M-B28	1.32	340.1
125	A2-M-B28	1.37	340.1
126	A8-M-B28	1.31	386.1
127	A3-M-B28	1.2	316.1
128	A1-M-B29	1.04	272.1
129	A1-M-B30	1.21	394.2
130	A9-M-B30	1.24	394.2
131	A2-M-B30	1.24	394.2
132	A6-M-B30	1.24	386.1
133	A7-M-B30	1.17	410.2
134	A4-M-B30	1.21	440.2
135	A1-M-B31	1.31	340.1
136	A9-M-B31	1.33	340.1
137	A2-M-B31	1.33	340.1
138	A6-M-B31	1.23	332.1
139	A8-M-B31	1.29	386.1
140	A7-M-B31	1.26	356.1

Entry	Compound	r.t (min)	[M+H] ⁺
141	A3-M-B31	1.18	316.1
142	A1-M-B32	1.28	322.1
143	A2-M-B32	1.3	322.1
144	A6-M-B32	1.21	314.1
145	A3-M-B32	1.16	298.1
146	A1-M-B33	1.3	284.2
147	A2-M-B33	1.33	284.2
148	A8-M-B33	1.29	330.2
149	A3-M-B33	1.17	260.1
150	A1-M-B34	1.51	326.2
151	A9-M-B34	1.54	326.2
152	A2-M-B34	1.53	326.2
153	A6-M-B34	1.42	318.2
154	A8-M-B34	1.48	372.2
155	A7-M-B34	1.44	342.2
156	A3-M-B34	1.38	302.2
157	A1-M-B35	1.33	382.0
158	A9-M-B35	1.34	382.0
159	A2-M-B35	1.34	382.0
160	A6-M-B35	1.24	374.0
161	A7-M-B35	1.26	398.0
162	A3-M-B35	1.19	358.0
163	A1-M-B36	1.28	324.1
164	A2-M-B36	1.31	324.1
165	A3-M-B36	1.16	300.1
166	A1-M-B37	1.44	346.2
167	A2-M-B37	1.47	346.2
168	A6-M-B37	1.51	338.1
169	A8-M-B37	1.43	392.2
170	A3-M-B37	1.32	322.1
171	A1-M-B38	1.52	376.2
172	A9-M-B38	1.55	376.2
173	A1-M-B39	1.29	397.2
174	A8-M-B39	1.28	443.2
175	A7-M-B39	1.25	413.2
176	A1-M-B40	1.28	340.1
177	A9-M-B40	1.3	340.1
178	A2-M-B40	1.3	340.1
179	A6-M-B40	1.2	332.1
180	A8-M-B40	1.27	386.1
181	A7-M-B40	1.23	356.1
182	A3-M-B40	1.15	316.1
183	A1-M-B41	1.38	382.0
184	A8-M-B41	1.37	428.1
185	A3-M-B41	1.25	358.0
186	A1-M-B42	1.32	318.2
187	A2-M-B42	1.34	318.2
188	A8-M-B42	1.31	364.2

Entry	Compound	r.t. (min)	[M+H] ⁺
189	A3-M-B42	1.19	294.1
190	A1-M-B43	1.21	302.1
191	A2-M-B43	1.24	302.1
192	A8-M-B43	1.21	348.1
193	A1-M-B44	1.33	336.1
194	A9-M-B44	1.36	336.1
195	A3-M-B44	1.21	312.1
196	A1-M-B45	1.4	352.1
197	A8-M-B45	1.39	398.1
198	A3-M-B45	1.29	328.1
199	A1-M-B46	1.39	310.2
200	A8-M-B46	1.38	356.2
201	A3-M-B46	1.27	286.1
202	A1-M-B47	1.28	282.2
203	A2-M-B47	1.28	282.2
204	A8-M-B47	1.25	328.2
205	A3-M-B47	1.12	258.1
206	A1-M-B48	1.27	284.2
207	A9-M-B48	1.3	284.2
208	A2-M-B48	1.3	284.2
209	A6-M-B48	1.19	276.1
210	A8-M-B48	1.26	330.2
211	A7-M-B48	1.22	300.2
212	A3-M-B48	1.14	260.1
213	A1-M-B49	1.39	362.2
214	A2-M-B49	1.42	362.2
215	A8-M-B49	1.38	408.2
216	A3-M-B49	1.28	338.1
217	A1-M-B50	1.13	285.2
218	A9-M-B50	1.34	285.2
219	A2-M-B50	1.18	285.2
220	A6-M-B50	1.05	277.1
221	A7-M-B50	1.1	301.2
222	A3-M-B50	1	261.1
223	A1-M-B51	1.33	333.2
224	A2-M-B51	1.37	333.2
225	A1-M-B52	1.41	397.1
226	A9-M-B52	1.44	397.1
227	A2-M-B52	1.45	397.1
228	A6-M-B52	1.35	389.0
229	A8-M-B52	1.42	443.1
230	A1-M-B53	1.31	349.2
231	A9-M-B53	1.31	349.2
232	A2-M-B53	1.31	349.2
233	A6-M-B53	1.21	341.1
234	A10-M-B54	1.26	392.1
235	A11-M-B55	1.41	374.1
236	A1-M-B56	1.05	271.1

Entry	Compound	r.t. (min)	[M+H] ⁺
237	A9-M-B56	1.09	271.1
238	A2-M-B56	1.09	271.1
239	A6-M-B56	0.97	263.1
240	A8-M-B56	1.08	317.2
241	A1-M-B57	1.4	325.2
242	A9-M-B57	1.33	325.2
243	A2-M-B57	1.33	325.2
244	A6-M-B57	1.23	317.1
245	A8-M-B57	1.31	371.2
246	A1-M-B58	1.28	355.1
247	A2-M-B58	1.31	355.1
248	A1-M-B59	1.28	337.1
249	A9-M-B59	1.32	337.1
250	A2-M-B59	1.32	337.1
251	A6-M-B59	1.22	329.1
252	A1-M-B60	1.39	353.1
253	A2-M-B60	1.43	353.1
254	A6-M-B60	1.33	345.0
255	A1-M-B61	1.24	349.2
256	A9-M-B61	1.27	349.2
257	A2-M-B61	1.27	349.2
258	A6-M-B61	1.17	341.1
259	A8-M-B61	1.25	395.2
260	A1-M-B62	1.47	361.2
261	A9-M-B62	1.5	361.2
262	A2-M-B62	1.5	361.2
263	A6-M-B62	1.41	353.1
264	A8-M-B62	1.48	407.2
265	A1-M-B63	1.27	347.2
266	A9-M-B63	1.3	347.2
267	A2-M-B63	1.3	347.2
268	A6-M-B63	1.35	339.1
269	A8-M-B63	1.29	393.2
270	A1-M-B64	1.36	353.1
271	A12-M-B64	1.34	369.1
272	A1-M-B65	1.38	353.1
273	A12-M-B65	1.38	369.1
274	A8-M-B65	1.4	399.1
275	A1-M-B66	1.32	337.1
276	A12-M-B66	1.32	353.1
277	A2-M-B66	1.49	337.1
278	A6-M-B66	1.26	329.1
279	A1-M-B67	1.3	313.2
280	A12-M-B67	1.29	329.2
281	A2-M-B67	1.34	313.2
282	A6-M-B67	1.23	305.1
283	A8-M-B67	1.32	359.2
284	A1-M-B68	1.23	361.2

Entry	Compound	r.t. (min)	[M+H] ⁺
285	A12-M-B68	1.22	377.2
286	A2-M-B68	1.27	361.2
287	A1-M-B69	1.33	347.2
288	A12-M-B69	1.32	363.2
289	A2-M-B69	1.36	347.2
290	A8-M-B69	1.34	393.2
291	A1-M-B70	1.33	351.2
292	A12-M-B70	1.31	367.1
293	A1-M-B71	1.57	347.2
294	A12-M-B71	1.38	363.2
295	A2-M-B71	1.41	347.2
296	A6-M-B71	1.31	339.1
297	A8-M-B71	1.39	393.2
298	A1-M-B72	1.35	355.1
299	A12-M-B72	1.35	371.1
300	A1-M-B73	1.22	361.2
301	A12-M-B73	1.21	377.2
302	A2-M-B73	1.26	361.2
303	A1-M-B74	1.52	392.1
304	A12-M-B74	1.49	408.1
305	A2-M-B74	1.54	392.1
306	A1-M-B75	1.37	359.1
307	A12-M-B75	1.35	375.1
308	A2-M-B75	1.4	359.1
309	A1-M-B76	1.36	400.1
310	A12-M-B76	1.35	416.1
311	A2-M-B76	1.4	400.1
312	A1-M-B77	1.49	374.1
313	A12-M-B77	1.46	390.1
314	A2-M-B77	1.52	374.1
315	A1-M-B78	1.43	374.1
316	A12-M-B78	1.41	390.1
317	A2-M-B78	1.46	374.1
318	A1-M-B79	1.28	306.1
319	A12-M-B79	1.27	322.1
320	A2-M-B79	1.32	306.1
321	A1-M-B80	1.51	380.0
322	A12-M-B80	1.49	396.0
323	A2-M-B80	1.55	380.0
324	A1-M-B81	1.18	382.2
325	A1-M-B82	1.37	365.1
326	A1-M-B83	1.23	311.2
327	A2-M-B83	1.27	311.2
328	A2-M-B84	1.19	278.1
329	A12-M-B85	1.42	370.1
330	A2-M-B85	1.47	354.1
331	A12-M-B86	1.47	390.1
332	A1-M-B87	1.51	418.0

Entry	Compound	r.t. (min)	[M+H] ⁺
333	A12-M-B87	1.75	434.0
334	A1-M-B88	1.2	292.1
335	A2-M-B88	1.24	292.1
336	A1-M-B89	1.39	358.1
337	A12-M-B89	1.37	374.1
338	A2-M-B89	1.42	358.1
339	A1-M-B54	1.36	346.1
340	A12-M-B54	1.34	362.1
341	A2-M-B54	1.4	346.1
342	A1-M-B55	1.41	358.1
343	A12-M-B55	1.39	374.1
344	A2-M-B55	1.44	358.1
345	A1-M-B90	1.52	424.0
346	A1-M-B91	1.32	400.1
347	A2-M-B91	1.36	400.1
348	A1-M-B92	1.42	358.1
349	A12-M-B92	1.4	374.1
350	A2-M-B92	1.45	358.1
351	A1-M-B93	1.44	354.1
352	A12-M-B93	1.42	370.1
353	A2-M-B93	1.47	354.1
354	A1-M-B94	1.49	448.0
355	A12-M-B94	1.46	464.0
356	A2-M-B94	1.52	448.0
357	A13-M-B1	1.24	336.1
358	A14-M-B1	1.3	318.2
359	A13-M-B2	1.3	350.1
360	A14-M-B2	1.41	332.2
361	A15-M-B3	1.44	324.2
362	A13-M-B3	1.38	342.2
363	A16-M-B3	1.42	340.2
364	A15-M-B5	1.58	338.2
365	A17-M-B5	1.35	360.0
366	A13-M-B5	1.48	356.2
367	A18-M-B5	1.28	300.2
368	A11-M-B5	1.47	340.2
369	A17-M-B6	1.21	373.9
370	A13-M-B6	1.36	370.1
371	A13-M-B7	1.29	380.1
372	A16-M-B7	1.34	378.2
373	A17-M-B8	1.08	384.0
374	A15-M-B10	1.43	312.2
375	A10-M-B10	1.22	344.2
376	A17-M-B10	1.19	334.0
377	A13-M-B10	1.36	330.2
378	A11-M-B10	1.33	314.2
379	A16-M-B10	1.41	328.2
380	A15-M-B11	1.35	336.1

Entry	Compound	r.t. (min)	[M+H] ⁺
381	A17-M-B11	1.12	358.0
382	A13-M-B11	1.28	354.1
383	A14-M-B11	1.38	336.1
384	A15-M-B12	1.29	353.1
385	A13-M-B12	1.22	371.1
386	A19-M-B12	1.15	369.1
387	A20-M-B12	1.29	377.0
388	A15-M-B13	1.32	324.1
389	A17-M-B13	1.07	345.9
390	A13-M-B13	1.25	342.1
391	A15-M-B14	1.25	378.2
392	A17-M-B14	1.02	400.0
393	A13-M-B14	1.18	396.1
394	A15-M-B15	1.24	282.2
395	A13-M-B15	1.16	300.1
396	A11-M-B15	1.14	284.1
397	A15-M-B16	1.32	348.2
398	A17-M-B16	1.09	370.0
399	A14-M-B16	1.35	348.2
400	A13-M-B17	1.14	288.1
401	A17-M-B18	1.18	376.0
402	A13-M-B18	1.34	372.1
403	A17-M-B19	1.1	370.0
404	A13-M-B19	1.25	366.1
405	A11-M-B19	1.23	350.1
406	A16-M-B19	1.3	364.2
407	A15-M-B20	1.23	337.2
408	A17-M-B20	0.95	359.0
409	A13-M-B20	1.15	355.1
410	A11-M-B20	1.14	339.1
411	A14-M-B20	1.26	337.2
412	A13-M-B21	1.27	354.1
413	A11-M-B21	1.25	338.1
414	A14-M-B21	1.38	336.1
415	A17-M-B23	1.23	368.0
416	A13-M-B23	1.36	364.1
417	A15-M-B25	1.4	352.1
418	A13-M-B25	1.3	370.1
419	A19-M-B25	1.24	368.1
420	A17-M-B26	1.04	365.0
421	A13-M-B26	1.22	361.1
422	A17-M-B27	1.07	318.0
423	A13-M-B27	1.26	314.1
424	A16-M-B27	1.31	312.2
425	A17-M-B28	1.2	376.0
426	A13-M-B28	1.33	372.1
427	A11-M-B29	1.02	288.1
428	A14-M-B29	1.16	286.1

Entry	Compound	r.t. (min)	[M+H] ⁺
429	A19-M-B29	0.99	302.1
430	A16-M-B29	1.1	302.1
431	A17-M-B95	1.22	373.9
432	A13-M-B95	1.37	370.1
433	A17-M-B31	1.16	376.0
434	A13-M-B31	1.32	372.1
435	A14-M-B31	1.41	354.1
436	A19-M-B31	1.25	370.1
437	A15-M-B32	1.37	336.1
438	A17-M-B32	1.12	358.0
439	A13-M-B32	1.29	354.1
440	A11-M-B32	1.26	338.1
441	A14-M-B34	1.6	340.2
442	A19-M-B34	1.42	356.2
443	A20-M-B34	1.58	364.2
444	A16-M-B34	1.54	356.2
445	A14-M-B90	1.62	438.0
446	A15-M-B96	1.6	404.1
447	A14-M-B35	1.42	396.1
448	A13-M-B36	1.29	356.1
449	A15-M-B37	1.52	360.2
450	A17-M-B37	1.31	382.0
451	A13-M-B37	1.44	378.2
452	A11-M-B37	1.42	362.2
453	A17-M-B38	1.4	412.0
454	A13-M-B38	1.52	408.2
455	A17-M-B97	1.36	416.0
456	A13-M-B97	1.47	412.1
457	A15-M-B40	1.37	354.1
458	A17-M-B40	1.12	376.0
459	A13-M-B40	1.28	372.1
460	A14-M-B40	1.38	354.1
461	A16-M-B40	1.33	370.1
462	A17-M-B41	1.23	417.9
463	A13-M-B41	1.37	414.0
464	A13-M-B42	1.32	350.1
465	A20-M-B45	1.48	390.0
466	A17-M-B46	1.25	346.0
467	A13-M-B46	1.4	342.2
468	A15-M-B47	1.33	296.2
469	A17-M-B47	1.08	318.0
470	A13-M-B47	1.27	314.1
471	A15-M-B48	1.35	298.2
472	A10-M-B48	1.14	330.2
473	A17-M-B48	1.1	320.0
474	A13-M-B48	1.28	316.1
475	A11-M-B48	1.26	300.2
476	A14-M-B48	1.39	298.2

Entry	Compound	r.t. (min)	[M+H] ⁺
477	A19-M-B48	1.21	314.1
478	A20-M-B48	1.36	322.1
479	A15-M-B50	1.21	299.2
480	A10-M-B50	1.04	331.2
481	A17-M-B50	0.94	321.0
482	A14-M-B50	1.25	299.2
483	A15-M-B51	1.4	347.2
484	A17-M-B51	1.19	369.0
485	A13-M-B51	1.34	365.1
486	A11-M-B51	1.33	349.2
487	A20-M-B51	1.43	371.1
488	A17-M-B52	1.29	432.9
489	A13-M-B52	1.42	429.0
490	A11-M-B52	1.42	413.1
491	A20-M-B52	1.51	435.0
492	A15-M-B53	1.35	363.2
493	A17-M-B53	1.13	385.0
494	A13-M-B53	1.29	381.1
495	A14-M-B53	1.39	363.2
496	A10-M-B56	0.97	317.2
497	A14-M-B56	1.18	285.2
498	A19-M-B56	1.02	301.1
499	A10-M-B57	1.21	371.2
500	A17-M-B57	1.16	361.0
501	A13-M-B57	1.31	357.2
502	A14-M-B57	1.41	339.2
503	A19-M-B57	1.27	355.2
504	A20-M-B57	1.41	363.1
505	A10-M-B58	1.2	401.1
506	A17-M-B58	1.13	391.0
507	A13-M-B58	1.3	387.1
508	A10-M-B59	1.22	383.1
509	A17-M-B59	1.14	373.0
510	A13-M-B59	1.31	369.1
511	A20-M-B59	1.4	375.1
512	A13-M-B60	1.41	385.1
513	A19-M-B60	1.37	383.1
514	A20-M-B60	1.5	391.0
515	A20-M-B62	1.57	399.1
516	A15-M-B63	1.36	361.2
517	A10-M-B63	1.19	393.2
518	A17-M-B63	1.13	383.0
519	A13-M-B63	1.29	379.2
520	A11-M-B63	1.28	363.2
521	A14-M-B63	1.39	361.2
522	A19-M-B63	1.25	377.2
523	A17-M-B64	1.22	389.0
524	A17-M-B65	1.26	389.0

Entry	Compound	r.t. (min)	[M+H] ⁺
525	A13-M-B65	1.4	385.1
526	A20-M-B65	1.49	391.0
527	A14-M-B66	1.43	351.2
528	A20-M-B66	1.43	375.1
529	A13-M-B98	1.29	376.1
530	A14-M-B67	1.42	327.2
531	A13-M-B68	1.25	393.1
532	A17-M-B69	1.21	383.0
533	A13-M-B69	1.35	379.2
534	A11-M-B69	1.32	363.2
535	A10-M-B70	1.25	397.2
536	A17-M-B70	1.18	387.0
537	A13-M-B70	1.34	383.1
538	A13-M-B72	1.36	387.1
539	A14-M-B84	1.28	292.1
540	A17-M-B87	1.38	453.9
541	A13-M-B88	1.22	324.1
542	A14-M-B88	1.32	306.1
543	A17-M-B74	1.39	427.9
544	A13-M-B75	1.37	391.1
545	A17-M-B76	1.24	436.0
546	A13-M-B76	1.37	432.1
547	A14-M-B76	1.47	414.1
548	A15-M-B99	1.69	410.2
549	A10-M-B99	1.51	442.2
550	A17-M-B99	1.51	432.0
551	A13-M-B99	1.62	428.1
552	A15-M-B77	1.56	388.1
553	A17-M-B77	1.35	409.9
554	A10-M-B78	1.33	420.1
555	A13-M-B78	1.43	406.0
556	A17-M-B79	1.1	342.0
557	A15-M-B80	1.58	394.0
558	A17-M-B80	1.37	415.9
559	A14-M-B80	1.62	394.0
560	A15-M-B81	1.65	396.2
561	A10-M-B81	1.47	428.2
562	A17-M-B81	1.47	418.0
563	A13-M-B81	1.58	414.1
564	A15-M-B100	1.44	354.1
565	A17-M-B100	1.22	376.0
566	A13-M-B100	1.38	372.1
567	A11-M-B100	1.37	356.1
568	A14-M-B100	1.47	354.1
569	A15-M-B54	1.44	360.1
570	A17-M-B54	1.21	381.9
571	A13-M-B54	1.36	378.0
572	A11-M-B54	1.34	362.1

Entry	Compound	r.t. (min)	[M+H] ⁺
573	A14-M-B54	1.47	360.1
574	A15-M-B55	1.49	372.1
575	A17-M-B55	1.27	393.9
576	A13-M-B55	1.4	390.1
577	A14-M-B55	1.5	372.1
578	A17-M-B90	1.38	459.8
579	A13-M-B90	1.51	455.9
580	A10-M-B96	1.4	436.1
581	A17-M-B96	1.4	426.0
582	A13-M-B96	1.51	422.1
583	A14-M-B96	1.61	404.1
584	A10-M-B101	1.49	454.0
585	A15-M-B91	1.4	414.1
586	A10-M-B91	1.22	446.1
587	A13-M-B91	1.32	432.1
588	A17-M-B102	1.43	459.9
589	A13-M-B102	1.54	456.1
590	A15-M-B92	1.49	372.1
591	A17-M-B92	1.27	393.9
592	A13-M-B92	1.42	390.1
593	A15-M-B103	1.66	422.0
594	A10-M-B103	1.47	454.0
595	A17-M-B93	1.3	390.0
596	A13-M-B93	1.44	386.1
597	A10-M-B94	1.38	494.0
598	A17-M-B94	1.36	483.9
599	A13-M-B94	1.49	480.0
600	A17-M-B104	1.4	443.9
601	A21-M-B105	1.25	288.1
602	A21-M-B106	1.4	376.1
603	A21-M-B8	1.23	352.1
604	A22-M-B105	1.22	270.2
605	A22-M-B107	1.17	256.1
606	A22-M-B8	1.2	334.1
607	A22-M-B108	1.49	346.2
608	A23-M-B1	1.49	346.2
609	A23-M-B105	1.52	326.2
610	A23-M-B3	1.63	352.2
611	A23-M-B5	1.74	366.2
612	A23-M-B7	1.54	390.2
613	A23-M-B107	1.47	312.2
614	A23-M-B10	1.62	340.2
615	A24-M-B1	1.36	346.1
616	A24-M-B105	1.39	326.1
617	A24-M-B3	1.49	352.1
618	A24-M-B4	1.16	284.1
619	A24-M-B7	1.42	390.1
620	A24-M-B107	1.34	312.1

Entry	Compound	r.t. (min)	[M+H] ⁺
621	A24-M-B106	1.5	414.1
622	A24-M-B8	1.35	390.1
623	A24-M-B109	1.44	360.1
624	A24-M-B10	1.48	340.1
625	A21-M-B11	1.28	326.1
626	A21-M-B110	1.49	410.0
627	A21-M-B18	1.33	344.1
628	A21-M-B19	1.24	338.1
629	A21-M-B111	1.19	274.1
630	A21-M-B21	1.26	326.1
631	A22-M-B11	1.24	308.1
632	A22-M-B110	1.47	392.0
633	A22-M-B15	1.12	254.1
634	A22-M-B18	1.3	326.1
635	A22-M-B19	1.21	320.1
636	A22-M-B111	1.15	256.1
637	A22-M-B21	1.23	308.1
638	A23-M-B13	1.5	352.1
639	A23-M-B15	1.42	310.2
640	A23-M-B17	1.39	298.2
641	A23-M-B18	1.56	382.2
642	A23-M-B19	1.49	376.2
643	A23-M-B111	1.46	312.2
644	A23-M-B112	1.54	326.2
645	A23-M-B21	1.5	364.2
646	A24-M-B11	1.39	364.1
647	A24-M-B110	1.64	448.0
648	A24-M-B13	1.37	352.1
649	A24-M-B15	1.28	310.1
650	A24-M-B17	1.25	298.1
651	A24-M-B18	1.44	382.1
652	A24-M-B19	1.37	376.1
653	A24-M-B111	1.32	312.1
654	A24-M-B112	1.41	326.1
655	A24-M-B21	1.39	364.1
656	A21-M-B113	1.31	344.1
657	A21-M-B24	1.34	352.1
658	A21-M-B25	1.31	342.1
659	A21-M-B27	1.25	286.1
660	A21-M-B28	1.32	344.1
661	A21-M-B30	1.21	398.1
662	A21-M-B31	1.32	344.1
663	A21-M-B32	1.28	326.1
664	A22-M-B113	1.28	326.1
665	A22-M-B25	1.29	324.1
666	A22-M-B27	1.2	268.1
667	A22-M-B28	1.29	326.1
668	A22-M-B30	1.17	380.2

Entry	Compound	r.t. (min)	[M+H] ⁺
669	A22-M-B31	1.27	326.1
670	A22-M-B32	1.25	308.1
671	A23-M-B113	1.53	382.2
672	A23-M-B23	1.61	374.2
673	A23-M-B24	1.57	390.2
674	A23-M-B25	1.56	380.1
675	A23-M-B27	1.51	324.2
676	A23-M-B30	1.45	436.2
677	A23-M-B31	1.55	382.2
678	A24-M-B113	1.42	382.1
679	A24-M-B23	1.48	374.1
680	A24-M-B24	1.46	390.1
681	A24-M-B25	1.44	380.1
682	A24-M-B27	1.37	324.1
683	A24-M-B28	1.44	382.1
684	A24-M-B30	1.34	436.1
685	A24-M-B95	1.48	380.1
686	A24-M-B31	1.43	382.1
687	A24-M-B32	1.4	364.1
688	A21-M-B114	1.3	352.1
689	A21-M-B115	1.54	444.1
690	A21-M-B34	1.49	330.2
691	A21-M-B116	1.3	352.1
692	A21-M-B40	1.27	344.1
693	A21-M-B117	1.48	376.0
694	A22-M-B114	1.27	334.1
695	A22-M-B115	1.53	426.1
696	A22-M-B34	1.47	312.2
697	A22-M-B38	1.5	362.2
698	A22-M-B39	1.26	383.1
699	A22-M-B40	1.24	326.1
700	A22-M-B118	1.12	280.1
701	A23-M-B33	1.56	326.2
702	A23-M-B114	1.54	390.2
703	A23-M-B115	1.74	482.2
704	A23-M-B34	1.75	368.3
705	A23-M-B36	1.52	366.2
706	A23-M-B38	1.74	418.2
707	A23-M-B116	1.54	390.2
708	A23-M-B39	1.52	439.2
709	A23-M-B40	1.52	382.2
710	A23-M-B118	1.42	336.2
711	A24-M-B33	1.41	326.1
712	A24-M-B114	1.42	390.1
713	A24-M-B115	1.64	482.1
714	A24-M-B34	1.63	368.2
715	A24-M-B36	1.39	366.1
716	A24-M-B116	1.41	390.1

Entry	Compound	r.t. (min)	[M+H] ⁺
717	A24-M-B40	1.4	382.1
718	A24-M-B41	1.48	424.0
719	A24-M-B118	1.28	336.1
720	A21-M-B119	1.35	376.0
721	A21-M-B120	1.36	394.1
722	A21-M-B50	1.12	289.1
723	A21-M-B121	1.27	323.1
724	A21-M-B51	1.33	337.1
725	A21-M-B53	1.29	353.1
726	A22-M-B119	1.32	358.0
727	A22-M-B120	1.32	376.1
728	A22-M-B50	1.09	271.1
729	A22-M-B121	1.24	305.1
730	A22-M-B51	1.31	319.1
731	A22-M-B53	1.26	335.1
732	A22-M-B122	1.22	285.2
733	A23-M-B119	1.59	414.1
734	A23-M-B120	1.59	432.2
735	A23-M-B44	1.54	378.2
736	A23-M-B45	1.63	394.2
737	A23-M-B49	1.57	404.2
738	A23-M-B50	1.38	327.2
739	A23-M-B51	1.56	375.2
740	A23-M-B53	1.51	391.2
741	A23-M-B122	1.49	341.2
742	A24-M-B120	1.48	432.1
743	A24-M-B44	1.43	378.1
744	A24-M-B46	1.5	352.1
745	A24-M-B50	1.24	327.1
746	A24-M-B121	1.37	361.1
747	A24-M-B51	1.43	375.1
748	A24-M-B53	1.38	391.1
749	A24-M-B122	1.37	341.1
750	A22-M-B56	1.02	257.1
751	A22-M-B57	1.27	311.2
752	A22-M-B123	1.43	373.1
753	A22-M-B59	1.27	323.1
754	A22-M-B124	1.09	271.1
755	A22-M-B60	1.38	339.1
756	A22-M-B125	1.23	323.1
757	A22-M-B126	1.31	319.1
758	A22-M-B61	1.21	335.1
759	A23-M-B56	1.31	313.2
760	A23-M-B58	1.51	397.2
761	A23-M-B124	1.38	327.2
762	A23-M-B127	1.81	497.2
763	A23-M-B125	1.5	379.2
764	A23-M-B128	1.58	429.2

Entry	Compound	r.t. (min)	[M+H] ⁺
765	A23-M-B61	1.46	391.2
766	A24-M-B56	1.16	313.1
767	A24-M-B58	1.38	397.1
768	A24-M-B123	1.54	429.1
769	A24-M-B124	1.24	327.1
770	A24-M-B60	1.49	395.1
771	A24-M-B127	1.7	497.1
772	A24-M-B125	1.37	379.1
773	A24-M-B126	1.43	375.1
774	A24-M-B128	1.46	429.1
775	A24-M-B61	1.34	391.1
776	A22-M-B62	1.45	347.2
777	A22-M-B129	1.21	319.1
778	A22-M-B63	1.24	333.2
779	A22-M-B66	1.3	323.1
780	A22-M-B67	1.27	299.2
781	A22-M-B130	1.25	333.2
782	A22-M-B131	1.38	333.2
783	A23-M-B129	1.44	375.2
784	A23-M-B63	1.49	389.2
785	A23-M-B64	1.61	395.2
786	A23-M-B132	1.62	405.2
787	A23-M-B67	1.5	355.2
788	A24-M-B62	1.56	403.2
789	A24-M-B133	1.43	411.1
790	A24-M-B66	1.42	379.1
791	A24-M-B132	1.51	405.1
792	A24-M-B70	1.43	393.1
793	A22-M-B134	1.34	351.1
794	A22-M-B135	1.38	333.2
795	A22-M-B88	1.15	278.1
796	A22-M-B74	1.49	378.0
797	A22-M-B76	1.34	386.1
798	A22-M-B136	1.35	356.1
799	A22-M-B99	1.58	382.2
800	A22-M-B78	1.4	360.0
801	A22-M-B137	1.41	362.1
802	A22-M-B138	1.53	394.0
803	A23-M-B134	1.59	407.2
804	A23-M-B135	1.63	389.2
805	A23-M-B88	1.44	334.2
806	A23-M-B74	1.72	434.1
807	A23-M-B76	1.57	442.2
808	A23-M-B136	1.6	412.2
809	A23-M-B99	1.8	438.2
810	A23-M-B78	1.64	416.1
811	A23-M-B137	1.67	418.1
812	A23-M-B138	1.78	450.1

Entry	Compound	r.t. (min)	[M+H] ⁺
813	A24-M-B135	1.51	389.1
814	A24-M-B86	1.61	416.0
815	A24-M-B74	1.63	434.0
816	A24-M-B76	1.4	442.1
817	A24-M-B136	1.43	412.1
818	A24-M-B99	1.74	438.1
819	A24-M-B78	1.47	416.0
820	A24-M-B138	1.66	450.0
821	A22-M-B79	1.24	292.1
822	A22-M-B139	1.43	394.1
823	A22-M-B140	1.32	306.1
824	A22-M-B100	1.33	326.1
825	A22-M-B54	1.32	332.0
826	A22-M-B55	1.37	344.1
827	A22-M-B141	1.5	376.1
828	A23-M-B79	1.48	348.2
829	A23-M-B81	1.74	424.2
830	A23-M-B139	1.63	450.1
831	A23-M-B100	1.62	382.2
832	A23-M-B54	1.54	388.1
833	A23-M-B55	1.59	400.1
834	A23-M-B141	1.67	432.2
835	A23-M-B103	1.82	450.1
836	A23-M-B89	1.57	400.1
837	A24-M-B79	1.41	348.1
838	A24-M-B81	1.71	424.1
839	A24-M-B54	1.48	388.0
840	A24-M-B141	1.62	432.1
841	A24-M-B142	1.34	348.1
842	A12-M-B83	1.23	327.2
843	A1-M-B84	1.14	278.1
844	A12-M-B84	1.13	294.1
845	A1-M-B85	1.44	354.1
846	A1-M-B86	1.49	374.1
847	A2-M-B86	1.52	374.1
848	A2-M-B87	1.6	418.0
849	A1-M-B143	1.37	354.1
850	A12-M-B143	1.35	370.1
851	A2-M-B143	1.4	354.1
852	A12-M-B88	1.18	308.1
853	A22-M-B86	1.47	360.0
854	A23-M-B86	1.72	416.1
855	A24-M-B85	1.53	396.1
856	A13-M-B101	1.6	440.0
857	A10-M-B92	1.31	404.1
858	A13-M-B103	1.58	440.0
859	A10-M-B93	1.33	400.1
860	A15-M-B104	1.6	422.0

Entry	Compound	r.t. (min)	[M+H] ⁺
861	A21-M-B3	1.37	314.2
862	A22-M-B106	1.37	358.1
863	A22-M-B109	1.28	304.1
864	A22-M-B10	1.32	284.2
865	A23-M-B11	1.52	364.2
866	A21-M-B95	1.37	342.1
867	A22-M-B23	1.35	318.2
868	A22-M-B95	1.34	324.1
869	A23-M-B28	1.56	382.2
870	A23-M-B32	1.53	364.2
871	A21-M-B41	1.36	386.0
872	A22-M-B33	1.25	270.2
873	A22-M-B116	1.28	334.1
874	A22-M-B41	1.34	368.0
875	A22-M-B117	1.45	358.0
876	A21-M-B44	1.33	340.1
877	A22-M-B44	1.3	322.1
878	A22-M-B58	1.25	341.1
879	A22-M-B127	1.6	441.1
880	A23-M-B66	1.54	379.2
881	A6-M-B1	1.15	296.1
882	A8-M-B3	1.37	356.2
883	A4-M-B4	1.03	288.1
884	A5-M-B4	1.03	248.1
885	A2-M-B12	1.27	339.1
886	A2-M-B15	1.19	268.1
887	A8-M-B15	1.15	314.1
888	A6-M-B16	1.17	326.1
889	A8-M-B16	1.24	380.2
890	A8-M-B17	1.12	302.1
891	A8-M-B19	1.24	380.2
892	A7-M-B19	1.2	350.1
893	A6-M-B26	1.17	321.1
894	A3-M-B30	1.12	370.1
895	A9-M-B32	1.3	322.1
896	A8-M-B32	1.27	368.1
897	A8-M-B35	1.3	428.1
898	A3-M-B38	1.41	352.2
899	A2-M-B41	1.39	382.0
900	A6-M-B41	1.29	374.0
901	A1-M-B144	1.29	364.2
902	A9-M-B144	1.31	364.2
903	A6-M-B144	1.22	356.1
904	A7-M-B144	1.24	380.2
905	A6-M-B42	1.24	310.1
906	A3-M-B43	1.08	278.1
907	A9-M-B49	1.45	362.2
908	A6-M-B51	1.27	325.1

Entry	Compound	r.t. (min)	[M+H] ⁺
909	A8-M-B51	1.34	379.2
910	A11-M-B96	1.5	406.1
911	A17-M-B101	1.47	443.9
912	A1-M-B98	1.27	344.1
913	A2-M-B98	1.3	344.1
914	A6-M-B98	1.2	336.1
915	A6-M-B68	1.15	353.1
916	A8-M-B70	1.33	397.2
917	A12-M-B82	1.35	381.1
918	A15-M-B1	1.33	318.2
919	A17-M-B2	1.15	354.0
920	A15-M-B8	1.3	362.1
921	A13-M-B8	1.24	380.1
922	A14-M-B8	1.34	362.1
923	A17-M-B9	1.15	370.0
924	A19-M-B14	1.13	394.1
925	A13-M-B16	1.25	366.1
926	A19-M-B16	1.2	364.1
927	A20-M-B18	1.41	378.1
928	A14-M-B19	1.36	348.2
929	A20-M-B20	1.24	361.1
930	A16-M-B20	1.21	353.2
931	A17-M-B24	1.2	384.0
932	A14-M-B24	1.44	362.2
933	A10-M-B37	1.32	392.2
934	A19-M-B40	1.22	370.1
935	A14-M-B42	1.42	332.2
936	A13-M-B43	1.22	334.1
937	A20-M-B44	1.41	374.1
938	A11-M-B81	1.57	398.1
939	A17-M-B49	1.27	398.0
940	A13-M-B50	1.14	317.1
941	A14-M-B52	1.52	411.1
942	A10-M-B100	1.27	386.1
943	A19-M-B59	1.27	367.1
944	A17-M-B61	1.08	385.0
945	A17-M-B62	1.37	397.0
946	A13-M-B62	1.49	393.2
947	A14-M-B65	1.49	367.1
948	A13-M-B67	1.31	345.2
949	A14-M-B69	1.44	361.2
950	A17-M-B82	1.23	401.0
951	A13-M-B87	1.51	450.0
952	A13-M-B143	1.37	386.1
953	A19-M-B143	1.32	384.1
954	A11-M-B88	1.19	308.1
955	A15-M-B74	1.59	406.1
956	A13-M-B74	1.51	424.0

Entry	Compound	r.t. (min)	[M+H] ⁺
957	A14-M-B99	1.72	410.2
958	A15-M-B79	1.37	320.1
959	A13-M-B79	1.29	338.1
960	A14-M-B79	1.4	320.1
961	A9-M-B1	1.26	304.1
962	A8-M-B1	1.23	350.1
963	A9-M-B2	1.34	318.2
964	A8-M-B2	1.29	364.2
965	A7-M-B2	1.25	334.1
966	A9-M-B3	1.41	310.2
967	A23-M-B85	1.68	396.2
968	A6-M-B4	0.94	234.1
969	A6-M-B7	1.22	340.1
970	A7-M-B7	1.24	364.2
971	A6-M-B15	1.07	260.1
972	A7-M-B15	1.1	284.1
973	A7-M-B22	1.26	312.2
974	A2-M-B24	1.39	348.2
975	A6-M-B24	1.29	340.1
976	A8-M-B24	1.37	394.2
977	A9-M-B27	1.31	282.2
978	A6-M-B27	1.19	274.1
979	A8-M-B27	1.27	328.2
980	A2-M-B29	1.09	272.1
981	A7-M-B29	1.01	288.1
982	A8-M-B30	1.24	440.2
983	A9-M-B33	1.33	284.2
984	A7-M-B33	1.25	300.2
985	A24-M-B88	1.31	334.1
986	A2-M-B144	1.31	364.2
987	A8-M-B144	1.28	410.2
988	A3-M-B144	1.17	340.1
989	A8-M-B44	1.34	382.1
990	A7-M-B46	1.37	326.2
991	A9-M-B47	1.31	282.2
992	A7-M-B47	1.23	298.1
993	A7-M-B49	1.38	378.2
994	A8-M-B50	1.18	331.2
995	A9-M-B51	1.36	333.2
996	A8-M-B59	1.3	383.1
997	A8-M-B60	1.4	399.1
998	A8-M-B64	1.37	399.1
999	A8-M-B66	1.34	383.1
1000	A8-M-B68	1.24	407.2
1001	A6-M-B72	1.28	347.1
1002	A8-M-B72	1.37	401.1
1003	A17-M-B1	1.09	340.0

Entry	Compound	r.t. (min)	[M+H] ⁺
1004	A15-M-B2	1.39	332.2
1005	A16-M-B14	1.23	394.2
1006	A14-M-B15	1.27	282.2
1007	A11-M-B23	1.36	348.2
1008	A13-M-B24	1.34	380.1
1009	A17-M-B25	1.15	373.9
1010	A17-M-B42	1.17	354.0
1011	A16-M-B43	1.27	332.1
1012	A19-M-B52	1.39	427.0
1013	A13-M-B122	1.26	331.2
1014	A13-M-B61	1.25	381.1
1015	A14-M-B61	1.36	363.2
1016	A19-M-B66	1.3	367.1
1017	A11-M-B98	1.27	360.1
1018	A17-M-B68	1.06	397.0
1019	A14-M-B68	1.34	375.2
1020	A19-M-B87	1.45	448.0
1021	A14-M-B75	1.47	373.1
1022	A11-M-B99	1.61	412.2
1023	A13-M-B77	1.48	406.0
1024	A11-M-B77	1.47	390.1
1025	A14-M-B77	1.58	388.1
1026	A14-M-B78	1.53	388.1
1027	A10-M-B90	1.41	470.0
1028	A14-M-B101	1.71	422.0
1029	A10-M-B102	1.44	470.1
1030	A17-M-B103	1.46	443.9
1031	A10-M-B104	1.42	454.0
1032	A13-M-B104	1.52	440.0
1033	A21-M-B1	1.23	308.1
1034	A21-M-B108	1.52	364.2
1035	A21-M-B109	1.31	322.1
1036	A21-M-B10	1.36	302.2
1037	A22-M-B1	1.19	290.1
1038	A22-M-B3	1.34	296.2
1039	A22-M-B4	0.99	228.1
1040	A22-M-B7	1.27	334.1
1041	A23-M-B8	1.47	390.2
1042	A21-M-B15	1.16	272.1
1043	A23-M-B110	1.77	448.1
1044	A21-M-B36	1.27	328.1
1045	A22-M-B46	1.36	296.2
1046	A23-M-B121	1.49	361.2
1047	A23-M-B126	1.54	375.2
1048	A22-M-B85	1.4	340.1

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